Evaluation of Pharmacokinetic Models for the Disposition of Lead (Pb) in Humans, in Support of Application to Occupational Exposure Limit Derivation

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14. ABSTRACT

The National Research Council (NRC) issued a report on the exposure of Department of Defense (DOD) personnel to lead (Pb) at firing ranges (NRC, 2013). In this report, they expressed the opinion that the current Occupational Safety and Health Administration (OSHA) Permissible Exposure Limit (PEL) was not sufficiently protective of DOD firing range personnel. A need has been identified by the Office of the Deputy Under Secretary of Defense (Installations and Environment) to derive of airborne Pb levels corresponding to the blood Pb levels (BLL) associated with various levels of concern identified by U.S. Army Public Health Command (USAPHC, 2014). Mechanistic models for prediction of blood Pb, such as biokinetic or physiologically-based pharmacokinetic (PBPK) models, are appropriate tools for such a task. The two models under consideration were similar in their ability to simulate BLL measured in the selected studies. The O'Flaherty model, however, more accurately described urinary vs. biliary clearance of Pb than the Leggett+ model, indicating that the O'Flaherty model will more accurately predict BLL in subpopulations with impairments in either mode of clearance. The O'Flaherty model, therefore, is recommended for use in future DOD applications to derive occupational exposure limits for Pb.

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Evaluation of pharmacokinetic models for the disposition of lead (Pb) in humans, in support of application to occupational exposure limit derivation

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ABSTRACT

The National Research Council (NRC) issued a report on the exposure of Department of Defense (DOD) personnel to lead (Pb) at firing ranges (NRC, 2013). In this report, they expressed the opinion that the current Occupational Safety and Health Administration (OSHA) Permissible Exposure Limit (PEL) was not sufficiently protective of DOD firing range personnel. A need has been identified by the Office of the Deputy Under Secretary of Defense (Installations and Environment) to derive of airborne Pb levels corresponding to the blood Pb levels (BLL) associated with various levels of concern identified by U.S. Army Public Health Command (USAPHC, 2014). Mechanistic models for prediction of blood Pb, such as biokinetic or physiologically-based pharmacokinetic (PBPK) models, are appropriate tools for such a task. The two models under consideration were similar in their ability to simulate BLL measured in the selected studies. The O'Flaherty model, however, more accurately described urinary vs. biliary clearance of Pb than the Leggett+ model, indicating that the O'Flaherty model will more accurately predict BLL in subpopulations with impairments in either mode of clearance. The O'Flaherty model, therefore, is recommended for use in future DOD applications to derive occupational exposure limits for Pb.

INTRODUCTION

The National Research Council (NRC) issued a 2013 report on the exposure of Department of Defense (DOD) personnel to lead (Pb) at firing ranges (NRC, 2013). In this report, they expressed the opinion that the current Occupational Safety and Health Administration (OSHA) Permissible Exposure Limit (PEL) was not sufficiently protective of DOD firing range personnel. At the request of the Office of the Deputy Under Secretary of Defense, the U.S. Army Public Health Command (USAPHC) prepared a report on Provisional Blood Lead Guidelines for Occupational Monitoring of Lead Exposure in the DOD (USAPHC, 2014). As the title indicates, the recommendations of the USAPHC report were framed as target blood levels (rather an external concentration), consistent with approaches of other organizations (American Conference of Governmental Industrial Hygienists [ACGIH], 2002; CDC, 2012a). A need has been identified by the Office of the Deputy Under Secretary of Defense to build off of the USAPHC report in order to address specifics of monitoring and medical health surveillance programs needed to implement the USAPHC recommendations. Specifically, members of the DOD Occupational Medicine and Industrial Hygiene Working Groups have requested the derivation of airborne Pb levels corresponding to the blood Pb levels (BLL) associated with various levels of concern identified by USAPHC. Mechanistic models for prediction of blood Pb, such as biokinetic or physiologically-based pharmacokinetic (PBPK) models, can readily incorporate multiple routes of exposure (e.g., baseline dietary exposure, plus occupational inhalation exposure). Mechanistic models, in contrast to regression models, are generally more amenable to extrapolation to exposure conditions that differ from those under which the model was parameterized (U.S. EPA, 2006). The Office of the Under Secretary of Defense (Installations and Environment), in consultation with representatives of the implementing Working Groups and the Tri Service Toxicology Consortium, has tasked the Naval Medical Research Unit Dayton (NAMRU-Dayton) with evaluating the available pharmacokinetic models which could be used to derive airborne Action Levels (AL) or occupational exposure limits (OEL) for Pb. This work was reviewed and approved by the Tri Service Toxicology Consortium.

BACKGROUND

Overview of Pharmacokinetic Models for Pb in Adult Humans

Contemporary pharmacokinetic models for Pb were described in the 2006 Air Quality Criteria document for Pb (U.S. EPA, 2006); the 2013 Integrated Science Assessment noted that there have been few advances in this particular area since the 2006 document, and thus they were not extensively discussed therein (U.S. EPA, 2013). Three models were discussed in U.S. EPA (2006), the Integrated Exposure Uptake Biokinetic (IEUBK) model, the Leggett model, and the O'Flaherty model. U.S. EPA describes the O'Flaherty model as having fewer Pb-specific parameters, and being more physiologically-based in its description of Pb disposition than the

Leggett model. All three models have been tested against individual human data, with the Leggett and O'Flaherty models having been tested against data from adults as well as children. The O'Flaherty model predicts slightly higher quasi-steady state BLL for a soil ingestion scenario tested by U.S. EPA (2006) (4.6 µg/dl for the O'Flaherty model vs. 4.1 µg/dl for the Leggett model for soil Pb of 1000 µg/g), suggesting that it is a modestly conservative model choice. Information regarding model parameter and input uncertainty and variability has not been incorporated into the Leggett model (U.S. EPA, 2006). While U.S. EPA (2006) notes that variability and uncertainty simulations have been conducted for the O'Flaherty model (Beck et al., 2001), the documentation in the Beck paper was limited, the code and other additional information was not available from Dr. Beck when this author (Dr. Sweeney) made inquiries previously (~2012), and Dr. O'Flaherty has retired and is not available for consultation. Because the IEUBK model is intended to describe the kinetics of Pb only in children age 7 or less (US EPA 1994a, 1994b), rather than adults, to whom OELs are applicable, this model was not further considered. The Leggett model has been updated since the U.S. EPA assessment (2013) by Vork et al. (2013), Office of Environmental Health Hazard Assessment, California Environmental Protection Agency (OEHHA, Cal EPA). This version of the Leggett model is referred to as "Leggett+".

O'Flaherty model

The O'Flaherty (1993) model for Pb is a physiologically-based model, similar in many respects to those popularized for application to industrial chemicals by Mel Andersen and coworkers (e.g., Ramsey and Andersen, 1984). Distinctive features of the O'Flaherty model are (1) the incorporation of a detailed, age-dependent, physiological descriptions of bone growth and remodeling for trabecular and cortical bone of the skeleton and (2) the calendar-year dependent exposure parameters. Since its development, the model has been applied to evaluation of data from smelter workers (Fleming et al., 1999; Beck et al., 2001), impact of osteoporosis (O'Flaherty, 2000), determination of bioavailability (Polak et al., 1996), and the effects of microgravity-accelerated bone loss (Garcia et al., 2013).

The ACSL model code for the O'Flaherty human model (received from Dr. Gary Diamond, SRC) was consistent with the code provided in O'Flaherty (2000). Simulations were conducted using acslX (version 3.0.2.1, AEgis Technologies Group, Inc.). These two sets of model code had some discrepancies from the model description in O'Flaherty (1993). Specifically, the parameters "K" and "L" in O'Flaherty (1993) are called KAPPA and LAMBDA in the model code. The allometric exponent for bone growth (relating bone growth to body weight) is reported as 1.02 in O'Flaherty (1993), but as 1.188 in the provided model code and O'Flaherty (2000). The tissue:plasma partition coefficients in O'Flaherty (1993) were 100 for liver, kidney, and other well-perfused tissues and 20 for poorly perfused tissues other than bone. In contrast, the tissue:plasma partition coefficients in the model code received from Dr. Diamond and in O'Flaherty (2000) were 50 for liver, kidney and other well-perfused tissues, and 2 for poorly-perfused tissues other than bone. Autopsy data summarized by U.S. EPA (2006) indicated a

skeletal muscle:liver ratio of 0.05, so the revised partition coefficients found in the code (Pb muscle: liver ratio of 2/50 = 0.04) likely provide a better description of the soft tissue distribution of Pb than the O'Flaherty (1993) model (muscle: liver ratio of 20/100 = 0.2). No communication of changes from original partition coefficients were discussed in subsequent publications of the O'Flaherty lead model (Beck et al., 2001; Fleming et al., 1999; O'Flaherty 1995, 1998, 2000; O'Flaherty et al., 1998; Polak et al., 1996), but the altered partition coefficient values were documented in a table of parameter values for the cynomolgus monkey (O'Flaherty et al., 1998) and in the code provided as a supplement to O'Flaherty (2000), as noted above.

An aspect of the O'Flaherty model that contrasts to the Leggett/Leggett+ model was the way calendar years are incorporated in the description of exposures. Birth year is a potential risk factor for Pb toxicity due to the formerly higher environmental levels of lead due to uses that have since been curtailed (e.g., leaded gasoline), particularly in the U.S. and other developed nations; average BLL in children 1-5 years of age has decreased from 15.1 µg/dl to 1.51 µg/dl over the 30 year period from 1976-1980 to 2007-2008 (NTP, 2012). Calendar years are used to compute the background inhalation and ingestion (e.g., food and water) of Pb in the O'Flaherty model (O'Flaherty, 1993). Having this information integrated into the model has the potential to simplify the simulation of Pb disposition of individuals born during periods of historically higher Pb exposure as compared to those born more recently. However, since the calendar year based exposure estimates were developed roughly two decades ago, it is appropriate to test whether the model can adequately describe current BLLs. Simulations were conducted to estimate 2009 BLLs (central tendency estimates) for women with different birth years, using the model parameter values of the O'Flaherty model (Figure 1). Comparative data were derived from the CDC's 2009-2010 National Health and Nutrition Examination Survey (NHANES) database (CDC, 2012b), with the assumption that all blood samples were collected in 2009. Sample weights were used to derive a population-weighted average BLL for each age group; 38 to 67 samples were available for each age group. A single sample was excluded; this sample was from an 18-year old woman and contained 11.3 µg Pb/dl blood, the highest concentration reported among the 1528 samples from 18-47 year-old women. Exclusion of this apparent outlier reduced the estimated average blood concentration for 18-year-old women from 1.02 to 0.611 µg/dl. (Note: standard statistical tests for outliers are not valid for this non-random database due to oversampling of targeted subpopulations.) The model fairly consistently overpredicted the measured BLL. The discrepancy indices (the maximum of predicted value/measured value or measured value/predicted value) ranged from 1.0 (birth year 1988) to 2.3 (birth year 1971), with a geometric mean discrepancy index (GMDI) of 1.5. The agreement is well below the maximum discrepancy recommended by the International Programme on Chemical Safety (IPCS, 2010) for PBPK model use in risk assessment—IPCS recommends that, on average, the difference between the model and the data should be no more than a factor of 2. In general, the agreement was better for birth years 1974-1991 (GMDI = 1.4) than birth years 1962-1973 (GMDI = 1.9).

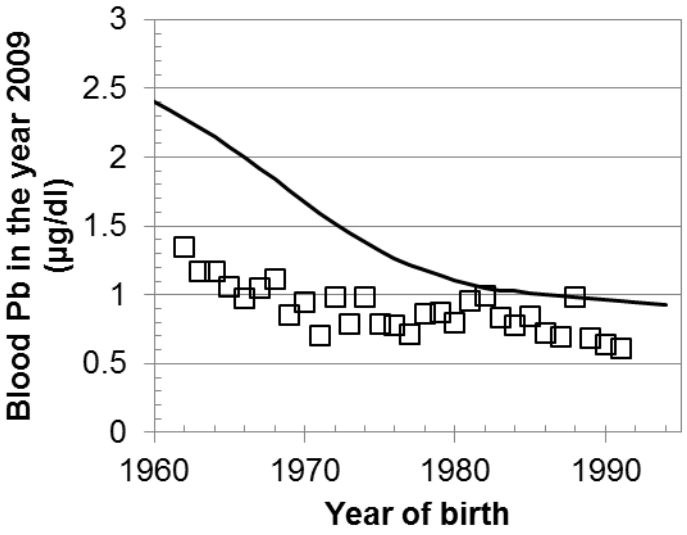

Figure 1. Central tendency estimates of blood lead levels in the year 2009 for U.S. women born between 1960 and 1995, simulated using the O'Flaherty (2000) model (line), and compared to NHANES 2009-2010 data (CDC, 2012b) (symbols).

Leggett+ model

The Leggett+ model was developed by Vork et al. (2013) as an update from the earlier ICRP/Leggett models. The ICRP/Leggett model (Leggett, 1993; Pounds and Leggett, 1998) was developed from models predominantly used in radiation protection, and is more commonly referred to as a "biokinetic" model rather than a "physiologically-based" model. The intercomparmental transfers in the ICRP/Leggett models are estimated primarily from empirical, chemical-specific data on transfer rates, rather than being based on physiological processes (such as blood flow) that can be measured (via appropriate markers) directly and adapted to specific, identified populations.

The Leggett+ model was developed from the Leggett/ICRP model explicitly for estimation of worker blood Pb levels. The strategy employed by Vork et al. (2013) was to adjust values of certain Leggett model parameters to improve fit to a subset of the available data (Hattis, 1981), and compare simulations, using the adjusted model parameter values, to other data sets.

PDF files containing the MATLAB model code for the Leggett+ model were downloaded from the Cal EPA website. The text in these files was used as the basis for an implementation of the Leggett+ model in acslX, prepared by the author of this report. Within this document, reproductions of simulations reported in Vork et al. (2013) will be denoted as "Leggett+ (MATLAB)", while simulations conducted with the NAMRU Dayton implementation of the Leggett+ model in acslX will be denoted as "Leggett+ (ACSL)."

Discrepancies between the text and figures of Vork et al. (2013) and the provided model code (PDFs) and a lack of transparency were identified. In the text, Vork et al. (2013) stated that they "adjusted and tested bone, blood, and plasma (via urine) [parameters]" (p. 49). While the "adjusted core model" blood and bone parameters are reported in the text (Table A-1, p. 56), the adjustment of the urinary clearance rate is not stated in the text. The adjustment value, "UCL = 0.25; % urine clearance setting" is noted in the model code (the "%" symbol marks the end of executable text in a line of MATLAB code), but no justification or other comments were provided. Figures show model-predicted concentrations in urine, but it was not clear from the publicly available code how these concentrations were derived. Mass balance equations for the urinary bladder were not a part of the Vork et al. (2013) model. The model includes a "urinary path" in the kidney and mass is transferred both from this urinary path and the diffusible plasma to a urinary bladder which is not a modeled compartment in Leggett+ (MATLAB). In Leggett+ (ACSL), a term was added to take the sum of these two transfer rates to the urinary bladder and divide by the urine output specified in the MATLAB code. (urine volume = body weight × 24/100, where BW is in kg and urine volume is in liters/day.

While the timing commands in the model code indicate that one year of simulation of "background" exposure (prior to elevated, occupational exposure) was used in at least some simulations, the depicted time courses for BLL and bone Pb in a worker exposed for 40 years (Vork et al., 2013 Figures 1, 2, and 3) appear to have a longer pre-employment simulation, perhaps 2 years. Pounds and Leggett (1998) report using simulations of 2000 days (~5.5 years) to achieve chronic, background pre-exposure levels for adults. The model code provides for the computation of initial adult Pb levels in various compartments, based on an initial BLL of 1.5 μg/dl. The basis for the proportions was not stated, and some compartments are initialized with no Pb. The basis may be the predicted distribution of lead at age 25 or 45 years after chronic life time exposure as predicted by the original Leggett model (Leggett, 1993, Table 3 therein). The proportions would be expected to be dose- and age-dependent (O'Flaherty, 1993). Considering how long it takes for new steady state levels to be achieved in the bone compartments (Vork et al., 2013, Figure 2 indicates that this process is incomplete after 40 years), the lack of information on how background distribution was estimated (at lower, current exposure levels) and the lack of information on how it was implemented for higher, historical exposures, lends uncertainty to the simulation of the calibration and validation data sets.

METHODS

Model simulations conducted for this report were performed using acslX (version 3.0.2.1, AEgis Technologies Group, Inc., Huntsville, AL).

When experimental data were not available in tabular form, data in figures were converted from graphical to numerical format using Paint (Version 6.1, Microsoft Corporation). Several data sets used by O'Flaherty (1993) and Vork et al. (2013) were used to demonstrate model performance. While only the Williams et al. (1969) data set can be explicitly identified as

having been used by both O'Flaherty (1993) and Vork et al. (2013) as part of model development/calibration/validation, additional data used by Leggett (1993) in the initial development of the ICRP/Leggett model were also used by O'Flaherty (1993) (Rabinowitz et al., 1976). When possible, the original publications of these data were retrieved, but in some cases were not available (explained in greater detail below, under "Results"). O'Flaherty (1993) frequently provided curves that plotted a fit to the original data (e.g., a cube root equation presented by the authors) rather than individual data. In attempting to recreate the simulations of O'Flaherty (1993), the preference has been to show comparisons to individual data, but this aim was not always achievable. Not all of the data sets considered by O'Flaherty (1993) and Vork et al. (2013) were utilized in the current assessment. For the O'Flaherty model in particular, it was found that the present model code did not always facilitate the simulation of some of the exposure regimens encountered in the underlying studies. Since multiple data sets were available, we considered it unlikely that the omission of these studies would affect overall conclusions about the two models, but the possibility cannot be completely ruled out. O'Flaherty (1993) does not provide a clear distinction among data sets used for calibration (i.e., data used to derive estimates of parameter values) vs. validation (i.e., where comparisons of model the model simulation and experimental data are used to "test" the model). Presumably, all presented data in O'Flaherty (1993) were used for "calibration", and none were reserved for a separate "validation" step. In contrast, Vork et al. (2013) clearly indicated that a subset of the Hattis data (1981) (data for workers with BLL > 60 μg/dl were excluded) were used for calibration, and the other data sets were used for validation. In this report, efforts to recreate the simulations conducted by the authors of the O'Flaherty (1993) paper and Vork et al. (2013) will be referred to as verification efforts. In addition to the data used in the development and evaluation of the O'Flaherty and Leggett+ models, data identified from U.S. EPA (2013) were used to assess the accuracy of the model predictions.

The initial model verification and validation efforts described in the initial draft of this report were conducted based strictly on publically available information. Subsequently, the author (Dr. Sweeney) contacted Dr. Kathleen Vork, who authored the OEHHA report. Dr. Vork provided MATLAB modeling files that provided additional, clarifying documentation of the modeling. NAMRU-Dayton simulations have not been redone to match the exact assumptions used by OEHHA. In general, the discrepancies were not large. One clarification (regarding concentration in urine) indicated that OEHHA was not using an appropriate metric to validate their model, and is addressed in the Results section.

RESULTS

Summary of data and model output used for model verification, calibration, and validation

Several data sets for the disposition of Pb in humans were used in the development of the two models under consideration, the Leggett+ model and its predecessors (Vork et al., 2013; Pounds and Leggett, 1998; Leggett, 1993 and the O'Flaherty (1993) model. In addition, relevant studies

on the relationship between blood and plasma Pb levels were identified from U.S. EPA (2013). A general characterization of the study, the data, and how the data were used, as well as delineation of available model outputs and other relevant comments are summarized in Table 1.

Hattis (1981)

Vork et al. (2013) used the Hattis (1981) data to recalibrate some of the parameters of the Leggett (1993) model as part of their development of the Leggett+ model, whereas O'Flaherty (1993) did not apparently use the Hattis (1981) data for model development or validation. While inspecting the Errata Sheet (October 2014) for Vork et al. (2013), noted discrepancies were found among some of the tabulated values for the last three columns: measured post-strike BLL, predicted post-strike BLL, and measured minus predicted BLL. These discrepancies occurred for individuals with equal duration of prestrike job tenure; the values for the final two columns were assumed to have been sorted incorrectly; by switching/rotating the paired values among the rows with equal job tenure (subjects 63, 73, and 474; 221 and 226; 45 and 47; 33, 34, and 39; and 8 and 15), the discrepancies could be eliminated. The corrected assignments of predicted post-strike BLL for Leggett+ (MATLAB) are presented in Table 3 and were used for the analyses that follow.

Unsuccessful attempts were made to verify the Leggett+ (MATLAB) post-strike BLL predictions using the Leggett+ (ACSL) model prior to achieving fairly similar values (Figure 2). For example, in the first attempt, the initial distribution of the body burden of Pb was unaltered from that in the Leggett+ (MATLAB) code, and a long (20+ years) pre-exposure simulation period was assumed. With these assumptions, the Leggett+ (ACSL) model consistently overpredicted the Leggett+ (MATLAB) post-strike outputs reported in Vork et al. (2013) by an average of 1.5 μg/dl. The Leggett+ (ACSL) model predictions were better able to replicate the Leggett+ (MATLAB) outputs when the initial adult body burden was increased, based on the reported individual pre-employment BLL, and the pre-occupational exposure simulation (at background intake) was decreased to the 2 years (similar to Vork et al., 2013, Figures 1-3). The overprediction of the Leggett+ (MATLAB) post-strike outputs by the Leggett+ (ACSL) model was 0.3 ± 0.7 μg/dl. Subsequent to the conduct of these simulations, Dr. Vork provided modeling scripts (Personal communication to Lisa Sweeney, September 15, 2015) that indicated that the duration of the OEHHA pre-occupation exposure simulation was 1 year, rather than 2 years as estimated by NAMRU Dayton.

Table 1. Human adult Pb data and model output used in model verification, calibration, and validation

Study name	Study description	Data description and availability	Use by O'Flaherty (1993)	Use for Leggett+ model or predecessors	Output availability (O'Flaherty or Leggett+ only)	Comments
Hattis (1981)	BLL was measured in 66 ASARCO smelter workers (Glover, MO) prior to and during active employment, and prior to returning to work after a 9-month strike in 1976	For 47 workers, individual values of pre-employment BLL, prestrike job tenure, pre-strike BLL, and post-strike BLL were available.	None identified	Used for Leggett+ model calibration by Vork et al. (2013). Workers with BLL > 60 μg/dl were excluded, leaving 47 individuals. Background and prestrike total exposure estimated from pre-employment and pre-strike BLL. Model parameters were adjusted to achieve improved agreement between measured and predicted post-strike BLL.	Leggett+ (MATLAB) post-strike BLL predictions reported in Vork et al. (2013) Table A-2 ("corrected", October 2014).	Report does not appear to be peer reviewed. Original study report not available to NAMRU-D. Vork et al. (2013) errata sheet still has errors. **See Table 2 of this document (correction of Vork et al. 2013, Table A-2), and Table 3, Figure 2, and Figure 3 of this document (new simulations).**
Manton and Cook (1984)	Samples were collected in Dallas, TX from 36 patients with neurological disease or symptoms. Occupation and source of Pb exposure were not characterized.	Serum Pb vs. blood Pb was plotted by the authors (Figure 2 of Manton and Cook, 1984). 26 individual values could be extracted from Manton and Cook by NAMRU-D; overlapping data points precluded extracting data at low serum Pb	One of three studies used to establish the binding capacity and portioning between plasma and erythrocytes (fit to this data set not shown by O'Flaherty).	One of two studies Vork et al. (2013) used to compare the plasma Pb vs. BLL relationship in the Leggett+ model to human observations	Leggett + (MATLAB) output was presented in Vork et al. (2013) Figure A-3.	**See Figures 4 and 5**.

Study name	Study description	Data description and availability	Use by O'Flaherty (1993)	Use for Leggett+ model or predecessors	Output availability (O'Flaherty or Leggett+ only)	Comments
Manton and Malloy (1983)	Not determined for this evaluation.	Paired urinary Pb excretion and blood Pb, and urinary excretion and plasma Pb in a single adult male	One of the 3 studies used by O'Flaherty to determine parameters for Pb binding in blood (blood vs. plasma data not shown, but could be inferred from figure).	None identified.	No O'Flaherty (1993) model output shown for urinary Pb excretion	Due to the availability of larger data sets, these data (from one individual) were not used in the current evaluation. Original study not retrieved.
DeSilva (1981)	Blood was obtained from 103 subjects in the Melbourne, Australia area. Subjects were referrals to the Health Commission from factories and private medical practitioners based on suspicion of elevated Pb and factory workers with more "moderate" exposure.	Paired plasma Pb and blood Pb concentrations in humans in O'Flaherty (1993), plasma and erythrocyte Pb in De Silva (1981).	One of the 3 studies (along with Manton and Cook, 1984 and Manton and Malloy, 1983) used by O'Flaherty to determine parameters for Pb binding in blood	None identified.	O'Flaherty (1993) Figure 4	Due to uncertainty about conversion of erythrocyte to whole blood Pb of DeSilva (1981) for O'Flaherty (1993) analysis and the availability of other plasma/blood data sets, these data were not used in the current evaluation.
Rabinowitz et al. (1976)	Five healthy men in a hospital metabolic unit (presumably in Los Angeles, CA) consumed known levels of dietary Pb; a stable Pb isotope was substituted for some of the dietary Pb for limited periods.	Tracer Pb concentrations were measured in blood several times (~weekly) during and after exposures of up to 124 days. Data for four subjects shown in O'Flaherty (1993)	Model calibration	Used by Leggett (1993) for model calibration.	Simulations for four individuals (O'Flaherty, 1993, Figure 11)	The models as received were not set up for tracer simulations in the presence of non-tracer Pb. Modifications necessary to complete such simulations were not undertaken.

Study name	Study description	Data description and availability	Use by O'Flaherty (1993)	Use for Leggett+ model or predecessors	Output availability (O'Flaherty or Leggett+ only)	Comments
Hirata et al. (1995)	Blood and urine samples were collected from 5 Japanese Pb workers over a 1 15-month period. Workers rotated among tasks with varying Pb exposure (highest Pb exposures were for 1 month at a time).	A total of 75 sets of samples were obtained for Pb measurement in whole blood, plasma, and urine, 15 at high exposure, 60 at low exposure. Data available as scatter plots in Hirata et al. (1995) and Vork et al. (2013).	None	One of two studies used to compare the plasma Pb vs. BLL relationship in the Leggett+ model to human observations. One of two studies used to compare urine Pb vs. BLL relationship in the Leggett+ model..	Leggett+ (MATLAB) output in Vork et al. (2013), Figure A-3 and A-4	**See Figures 4-7**
Schütz et al. (1996)	Human samples were collected to evaluate a new technique for measurement of Pb in human blood and plasma.	Blood and plasma Pb were measured in samples from 43 male Pb smelter workers (age 20-65, median: 35) and 7 controls (age 35-39; median: 41) from southern Sweden.	None	None	Not applicable	**See Figure 5b**
Hernández-Avila et al. (1998)	The relationship between plasma, blood, and bone levels was investigated in healthy individuals without occupational exposure.	Blood, plasma, tibia, and patella Pb levels were measured in 26 individuals with no known occupational exposure in Mexico City. The 26 participants included 20 women (age 24-54 years, mean: 36) and 6 men (age 19-70 years; mean: 38); only 5 participants were older than 50 years of age.	None	None	Not applicable	**See Figure 5b**

Study name	Study description	Data description and availability	Use by O'Flaherty (1993)	Use for Leggett+ model or predecessors	Output availability (O'Flaherty or Leggett+ only)	Comments
Manton et al. (2001)	The relationship between serum and blood Pb was investigated in 73 Los Angeles women of child bearing age.	The subjects ranged in age from 16-47, with a mean age of 29 years, with an average number of 3 pregnancies; on average, blood was collected 12 weeks after delivery. Approximately 70% of the participants were immigrants from Latin America. Due to some overlap in the source figure, 67 values were extracted.	None	None	Not applicable	**See Figure 5b**
Lee (1982)	Blood and urine samples were collected from 234 male Pb workers (age 28.4 ± 6.5 years [mean ± SD]) employment duration 4.4 ± 3.8 years) in Korea in 5 work areas, in which airborne Pb was measured 5 times.	In Lee (1982), the relationship of urine Pb to BLL was presented graphically for various ranges of BLL; urinary Pb was shown as mean ± 1 SD. Numbers of workers in various BLL bins were listed in a table. Volk et al. (2013) plotted the same information with three symbols (mean – 1 SD, mean, mean +1 SD) that sometimes overlapped.	None	One of two studies used to compare urine Pb vs. BLL relationship in the Leggett+ model.	Leggett+ (MATLAB) output in Vork et al. (2013), Figure A-4	**See Figures 6 and 7**

Study name	Study description	Data description and availability	Use by O'Flaherty (1993)	Use for Leggett+ model or predecessors	Output availability (O'Flaherty or Leggett+ only)	Comments
Williams et al. (1969)	Personal Pb samplers were worn by 30 Pb-exposed workers and 10 "controls" (with measurable exposure) for two weeks, presumably in England. One exposed worker withdrew from the study due to injury. Blood samples for Pb analysis were collected between 100 and 1100 hrs during the second week of exposure monitoring.	A scatter plot of BLL vs. Pb in air for 19 Pb-exposed workers and10 controls was available in Williams et al. (1969) and used for the present evaluation. Vork et al. (2013) also extracted and reported data for individuals with BLL <60 µg/dl. BLLs by job (Williams et al., 1969, Table 3) allow the computation of the "background" BLL.	Model calibration	Leggett+ model validation; subjects with BLL >60 µg/dl excluded, leaving 10 controls, and 6 workers with elevated Pb exposure.	O'Flaherty (1993), Figure 7. Vork et al. (2013) Table B-8.	When Vork et al. (2013) excluded workers with BLL >60 µg/dl, 6 workers with air Pb lower than that of the most highly-exposed retained workers were among excluded. Thus the remaining workers do not fully characterize the observed BLL vs. air Pb relationship in that range. **See Figure 8.**
Azar et al. (1975)	Personal air sampling devices were used. Participants were 30 subjects per location from 5 geographic locations and representing a range of exposure levels . Blood Pb and urine Pb were measured.	Tabular data for all subjects, grouped by geographic location and occupational setting, were available in Azar et al. (1975).	Model calibration	None identified	O'Flaherty (1993) Figure 8.	**See Figure 9.**
Griffin et al. (1975)	Human volunteers (prisoners in Dannemora, NY) were exposed ~23 hrs/day in an environmentally-controlled ward of a prison hospital, converted to serve as an exposure chamber. Blood was collected prior to, during, and after cessation of exposure to airborne Pb	Tabular data were available on individual volunteer ages, exposure dates, and individual blood Pb concentrations. Weekly average airborne Pb concentrations were also presented in tabular form.	None identified.	Vork et al. (2013) and Pounds and Leggett (1998); model validation.	Leggett+ (MATLAB) output in Vork et al. (2013) Table B-8.	**See Figures 10-12**

Study name	Study description	Data description and availability	Use by O'Flaherty (1993)	Use for Leggett+ model or predecessors	Output availability (O'Flaherty or Leggett+ only)	Comments
Gross (1979)	Pb was ingested or inhaled under controlled conditions by human subjects in the "Kehoe" balance studies	Pre-exposure, end of exposure, and end of post exposure observed BLL for 16 subjects (4 oral, 12 inhalation) available in O'Flaherty (1993), but exposure conditions not described	Model calibration	None identified	Simulated BLL of O'Flaherty (1993) available for the same 16 subjects for which data were presented in the same paper (Table 3)	The original study was not available. Some additional information was available in Gross (1981), but insufficient to consistently correlate individual BLLs to specific exposure scenarios, as may individuals had multiple exposures.
Cools et al. (1976)	Male volunteers (n =11, ages 20-30 years old, presumably Dutch) ingested Pb acetate in capsules or placebos. BLL was measured before and during the dosing period. Initial ingestion rate of 30 μg/day was adjusted once an individual's BLL reached 40 μg/dl.	Group average BLL for 3 pre-exposure dates and 9 days during the 49 exposure period were presented graphically; range was shown for 3 means. Daily average Pb dose was also presented graphically in Cools et al. (1976).	Model calibration	None identified	O'Flaherty (1993), Figure 10	The exposure pattern in Cools et al. (1976) could not readily have been produced using the currently available O'Flaherty code. **See Figures 13-14.**
Moore et al. (1977)	The relationship between household water used for drinking and food preparation and BLL in Scotland was evaluated. Those working in Pb-related industries were excluded from the study	A scatter plot of BLL and water Pb (n= 949) was presented in Moore et al. (1977). A plot of mean BLL vs. water Pb for 9 intervals of water Pb was used as the source of data for the current evaluation.	Model calibration	None identified	O'Flaherty (1993), Figure 5.	Some uncertainty with respect to drinking water ingestion rate was identified attempting to reproduce the O'Flaherty (1993) simulations.

Study name	Study description	Data description and availability	Use by O'Flaherty (1993)	Use for Leggett+ model or predecessors	Output availability (O'Flaherty or Leggett+ only)	Comments
Sherlock et al. (1982)	The relationship between household water used for drinking and food preparation in Ayr, Scotland, and BLL in adult women was evaluated in December, 1980.	The authors developed a cube-root equation to describe the water-BLL relationship. Individual data or data for sufficiently small could not be extracted due to the binned format for water and blood Pb ranges. .	Model calibration	None identified	O'Flaherty (1993) Figure 6.	**See Figure 15.**
Van de Vyver et al. (1988)	The relationship between blood Pb and Pb in the iliac crest was evaluated in samples collected via biopsy from 32 "at risk patients, including 21 lead workers". These subjects were a subset of the participants in a larger study (n = 153; 66 Belgian, 59 German, 28 French)	A scatter plot of bone Pb and BLL was presented in Van de Vyver et al. (1988).	Model calibration	None identified	O'Flaherty (1993) Figure 14	**See Figure 16.**
Nie et al. (2005)	Tibia and calcaneus bone Pb was measured in twice in 5 years in occupationally exposed workers; BLLs were also available for these workers. Data and simulations were conducted for a subset of 9 workers.	Blood Pb levels were only presented for one individual. Bone data (measured and simulated) were presented in tabular form for the 9 workers in the modeled subset.	None identified.	Model validation. Worker intake was estimated for multiple work periods based on BLL.	Simulations from the Leggett (1993) model and Nie's adjusted model are presented in Nie et al. (2005). Leggett+ model predictions are reported for Subject #1 at 4 years after retirement. It is unclear why only one set of bone Pb measurements was predicted.	Given the small data set (2 measurements in one individual), these data were not used in our evaluation.

Table 2. Hattis (1981) data and simulations used for calibration of the Leggett+ (MATLAB) model (corrections of October 2014 Errata sheet to Vork et al., 2013 indicated by shading)

Subject	Prestrike job tenure (days)	Measured preemployment BLL(μg/dL)	Estimated pre-strike BLL (μg/dL)	Measured post-strike BLL (μg/dL)	Predicted post-strike BLL (μg/dL)	Measured minus predicted BLL (μg/dL)
91	742	16	42.9	33	26	7
237	1106	36	54.8	39	44	-5
227	1148	18	54.3	34	34	0
218	1162	14	34.1	23	21	2
202	1288	26	60.4	47	42	5
191	1499	19	39	31	27	4
177	1582	35	55.4	40	44	-4
161	1617	21	46.7	22	31	-9
106	1818	17	37.8	24	25	-1
101	1953	22	52.1	37	35	2
88	1959	14	37.8	26	23	3
63	1960	20	42.4	34	29	5
73	1960	20	32.2	31	25	6
474	1960	17	38.5	31	25	6
299	2247	13	47.8	27	28	-1
6	2266	14	38.2	36	23	13
288	2266	27	43.3	40	34	6
286	2268	12	41.8	28	24	4
257	2346	34	41.6	36	38	-2
225	2408	26	52.2	47	37	10
221	2415	20	43.7	39	30	9
226	2415	10	36.5	33	20	13
203	2485	16	55.2	26	34	-8
188	2541	24	41	39	31	8
159	2653	18	49.5	38	32	6
158	2660	26	42.4	36	33	3
157	2667	27	54.5	31	39	-8
115	2912	33	45.8	35	39	-4
138	2928	10	52.4	21	30	-9
108	2979	33	43.9	40	38	2
67	3043	18	42.5	26	28	-2
62	3045	17	56.1	35	36	-1
68	3045	24	57.4	40	39	1
59	3052	13	46.7	23	28	-5
54	3060	34	43.9	38	39	-1
45	3066	22	52.3	37	35	2

Subject	Prestrike job tenure (days)	Measured preemployment BLL(μg/dL)	Estimated pre-strike BLL (μg/dL)	Measured post-strike BLL (μg/dL)	Predicted post-strike BLL (μg/dL)	Measured minus predicted BLL (μg/dL)
47	3066	24	35.8	29	29	0
36	3070	35	49.9	44	42	2
33	3071	21	39.9	24	29	-5
34	3071	17	26.7	20	21	-1
39	3071	13	39.3	20	24	-4
14	3077	20	37.3	28	27	1
8	3080	10	57	41	34	7
15	3080	10	35.3	10	20	-10
5	3084	11	30.5	17	18	-1
27	3084	20	34.1	32	26	6
23	3087	10	37.2	10	21	-11
Average	**2433**	**20.4**	**44.3**	**31.4**	**30.6**	**0.9**
Standard error	**98.3**	**1.1**	**1.2**	**1.3**	**1.0**	**0.9**

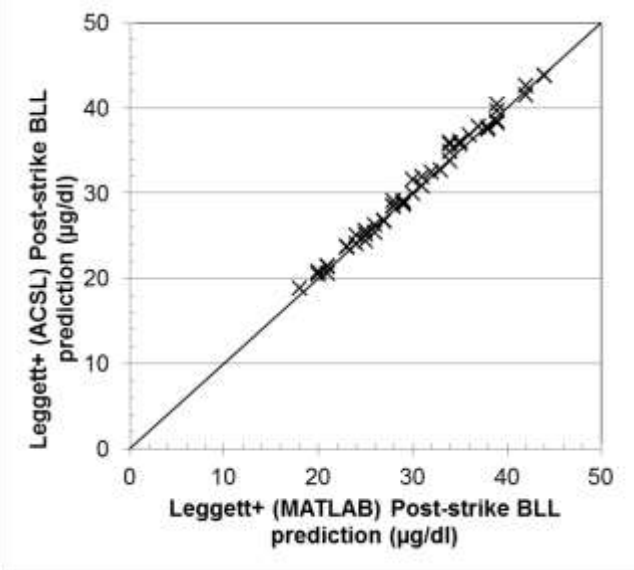

Figure 2. Comparison of predictions of Hattis (1981) post-strike BLL for two versions of the Leggett+ model. × Pairs of model predictions. The plotted unity line (intercept = 0, slope = 1) represents where all of the paired model predictions would lie if there was perfect agreement between the two models.

To simulate the Hattis (1981) data with the O'Flaherty model, assumptions about the age of the subjects had to be made. Age at the time of the strike was assumed to be 30 years. Since the strike was known to have occurred in 1976, that made the 1946 the birth year for all subjects. To calibrate pre-employment BLL, the background ingestion of Pb in food (assumed constant

throughout adulthood, including employment and the strike) for each individual was adjusted. The ambient air concentration for the employment period was then adjusted for each individual to match the pre-strike BLL. The resulting post-strike predictions are presented in Table 3.

Table 3. Hattis (1981) data and simulations of the O'Flaherty model

Subject	Prestrike job tenure (days)	Measured preemployment BLL(μg/dL)	Estimated pre-strike BLL (μg/dL)	Measured post-strike BLL (μg/dL)	Predicted post-strike BLL (μg/dL)	Measured minus predicted BLL (μg/dL)
91	742	16	42.9	33	22	11
237	1106	36	54.8	39	41	-2
227	1148	18	54.3	34	29	5
218	1162	14	34.1	23	19	4
202	1288	26	60.4	47	37	10
191	1499	19	39	31	25	6
177	1582	35	55.4	40	42	-2
161	1617	21	46.7	22	29	-7
106	1818	17	37.8	24	24	0
101	1953	22	52.1	37	33	4
88	1959	14	37.8	26	22	4
63	1960	20	42.4	34	28	6
73	1960	20	32.2	31	24	7
474	1960	17	38.5	31	24	7
299	2247	13	47.8	27	26	1
6	2266	14	38.2	36	23	13
288	2266	27	43.3	40	33	7
286	2268	12	41.8	28	23	5
257	2346	34	41.6	36	37	-1
225	2408	26	52.2	47	36	11
221	2415	20	43.7	39	29	10
226	2415	10	36.5	33	20	13
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188	2541	24	41	39	31	8
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157	2667	27	54.5	31	38	-7
115	2912	33	45.8	35	39	-4
138	2928	10	52.4	21	29	-8
108	2979	33	43.9	40	38	2
67	3043	18	42.5	26	28	-2
62	3045	17	56.1	35	34	1
68	3045	24	57.4	40	39	1

Subject	Prestrike job tenure (days)	Measured preemployment BLL(μg/dL)	Estimated pre-strike BLL (μg/dL)	Measured post-strike BLL (μg/dL)	Predicted post-strike BLL (μg/dL)	Measured minus predicted BLL (μg/dL)
59	3052	13	46.7	23	27	-4
54	3060	34	43.9	38	39	-1
45	3066	22	52.3	37	35	2
47	3066	24	35.8	29	29	0
36	3070	35	49.9	44	42	2
33	3071	21	39.9	24	29	-5
34	3071	17	26.7	20	21	-1
39	3071	13	39.3	20	24	-4
14	3077	20	37.3	28	27	1
8	3080	10	57	41	32	9
15	3080	10	35.3	10	20	-10
5	3084	11	30.5	17	19	-2
27	3084	20	34.1	32	26	6
23	3087	10	37.2	10	21	-11
Average	**2433**	**20.4**	**44.3**	**31.4**	**29.6**	**1.9**
Standard error	**98.3**	**1.1**	**1.2**	**1.3**	**1.0**	**0.9**

As can be seen from the averages presented in Tables 2 and 3, the Leggett+ model, which was calibrated to the Hattis (1981) data, has slightly better agreement with the data than the O'Flaherty model in terms of average predictions and post-strike value (1.9 ± 0.9 vs. 0.9 ± 0.9 μg/dl). When the absolute value of the difference between the modeled and predicted values are considered, the gap narrows. The Leggett+ (MATLAB) model differs from the experimental data by 4.8 ± 0.5 μg/dl, while the O'Flaherty model differs from the experimental data by 5.2 ± 0.5 μg/dl. The agreement between the measured and predicted values of both the Leggett+ and O'Flaherty models are depicted graphically in Figure 3. It is the judgment of the author of this report that the difference in the quality of fit between the models is small, but the fit to the Leggett+ model is marginally better.

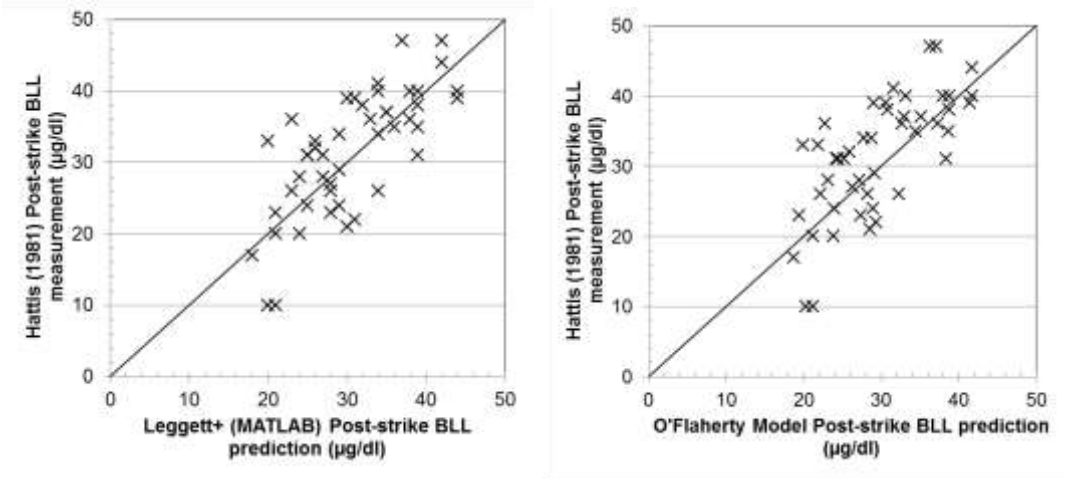


Figure 3. Comparison of Hattis (1981) post-strike BLL measurements to predictions of the Leggett+ model (MATLAB) (a) and O'Flaherty model (b). The plotted unity line (intercept = 0, slope = 1) represents where all of the comparisons of experiment vs. model predictions would lie if there was perfect agreement between the model and data.

Manton and Cook (1984), Hirata et al. (1995), Lee (1982), Schütz et al. (1996), Hernández-Avila et al. (1998), and Manton et al. (2001)

Data from Manton and Cook (1984), Hirata et al. (1995) and Lee (1982) were used by Vork et al (2013) as a basis with which to compare the Leggett+ (MATLAB) outputs for plasma Pb vs. BLL and urine Pb vs. BLL. It was not clear how the Leggett+ (MATLAB) simulations were conducted or how the urine concentration was computed, as the available code does not have a bladder per se. For the NAMRU-D attempts to recreate the Leggett+ simulations, the urine concentration was estimated from transfer rates out of diffusible plasma and the urinary path (portion of the kidney) divided by the urine output rate specified in the model code (0.24 L/d per kg BW = 1.752 L/d for the baseline simulation of a 73-kg human). The Leggett+ (ACSL) simulations to estimate BLL, plasma Pb, and urine Pb in exposed adults were conducted in two steps. In the first step, 2 years of adult baseline exposure with background intake of 6 µg/d and initial BLL of ~5 µg/dl was simulated, in accordance with the lowest levels reported in the studies. Then, as a second step, 10 years of varying levels of elevated exposure were simulated. Pb in blood, plasma, and urine at the end of the second step of the simulation were used to develop curves describing the relationships of BLL to plasma and urine Pb levels. The O'Flaherty model simulations to generate similar curves for an adult at age 30 years old were conducted for an adult born in 1953 with varying rates of Pb ingestion in food as an adult. The O'Flaherty model also does not simulate a urine concentration per se, but the rate of excretion via the kidney was divided by a urine production rate from the NHANES 2009-2012 data (54.5 ml/hr [1.3 L/day] for 20-39 year old males, Hays et al., 2015).

For comparison, the Vork et al. (2013) figures are reproduced below (Figures 4 and 6), each followed by a corresponding figure with the O'Flaherty and Leggett+ (ACSL) output (Figures 5 and 7). Figure 4 and the upper panel of Figure 5 are somewhat misleading with respect to the Manton and Cook (1984) data; the data that could not be individually extracted were in the ~5-18 ug/dl BLL range, with plasma Pb levels lower than the extractable points. The plasma Pb vs. BLL relationships for the Leggett+ (MATLAB) and Leggett+ (ACSL) models appear to be similar, but the lack of gridlines and tick marks in the Vork et al. (2013) figures make them harder to interpret. The two models' predictions of plasma Pb and BLL were similar at the lower BLLs relevant to OEL development, however the O'Flaherty model does a better job at predicting the higher BLL data (Figure 5, upper). To remedy the relative lack of extractable individual data in the lower, more relevant BLL range, more recent data from Schütz et al. (1996), Hernández-Avila et al. (1998), and Manton et al. (2001) (>90% extractable) were added to the figure, the incompletely extracted data of Manton and Cook (1984) were removed, the x-axis was truncated, and the y-axis was converted to log-scale to improve clarity.

The urine concentrations of the O'Flaherty model are at the low end of the data for similar BLL (Figure 7). The estimated urine concentrations from the Leggett+ (ACSL) model are much lower than the values reported for the Leggett+ (MATLAB) model (Figure 6 vs. Figure 7). As was previously noted, it was not clear in the publically available materials how Vork et al. (2013) calculated urinary concentrations. In a modeling script provided by Dr. Vork (personal communication to Lisa Sweeney, September 16, 2015), it is specified that the urine Pb concentration was calculated by taking the Pb concentration in the urinary path compartment and dividing it by the daily production of urine. This calculation is the same as assuming that there is exactly 100% turnover in this tissue compartment on a daily basis, and no other source of urinary Pb. As noted in the "Background" section above, the "urinary path" in the Leggett+ model is a region of the kidney. In this model, some of the Pb in the diffusible plasma is transferred to the urinary path at a rate described in the model, and Pb is cleared from the urinary path to the urinary bladder. Additional Pb is cleared directly from the diffusible plasma to the urinary bladder. The urine output is not used in the model as the clearance rate for the urinary path portion of the kidney. Based on this clarifying information, the Vork et al. (2013) finding that their predicted "urinary" concentrations correspond well to the data of Hirata et al. (1995) and Lee (1982) is not supportive of the validity of the model, since they did not compute urinary concentrations correctly.

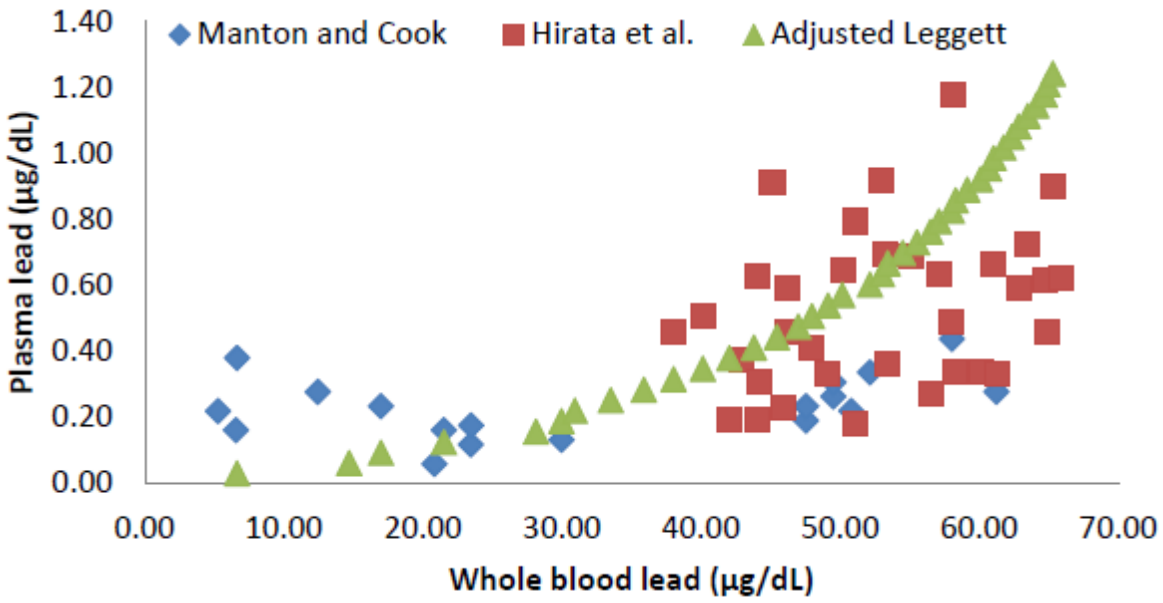
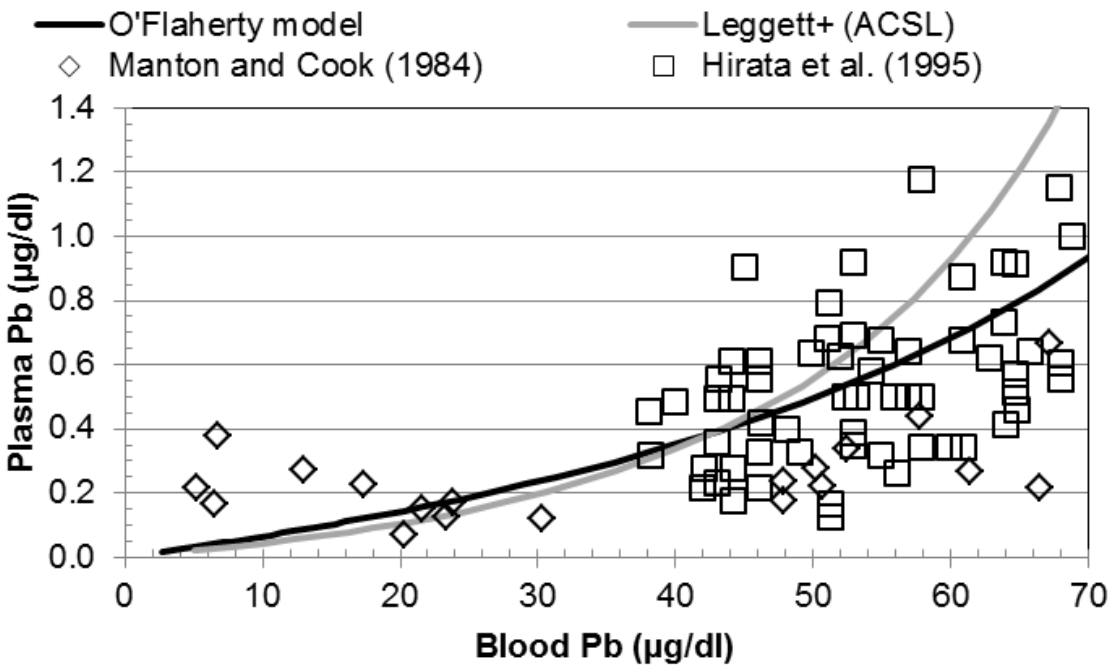


Figure 4. Plasma Pb versus whole blood Pb concentration—predictions from the adjusted Leggett model and data from two worker cohorts (Vork et al., 2013, Figure A-3).



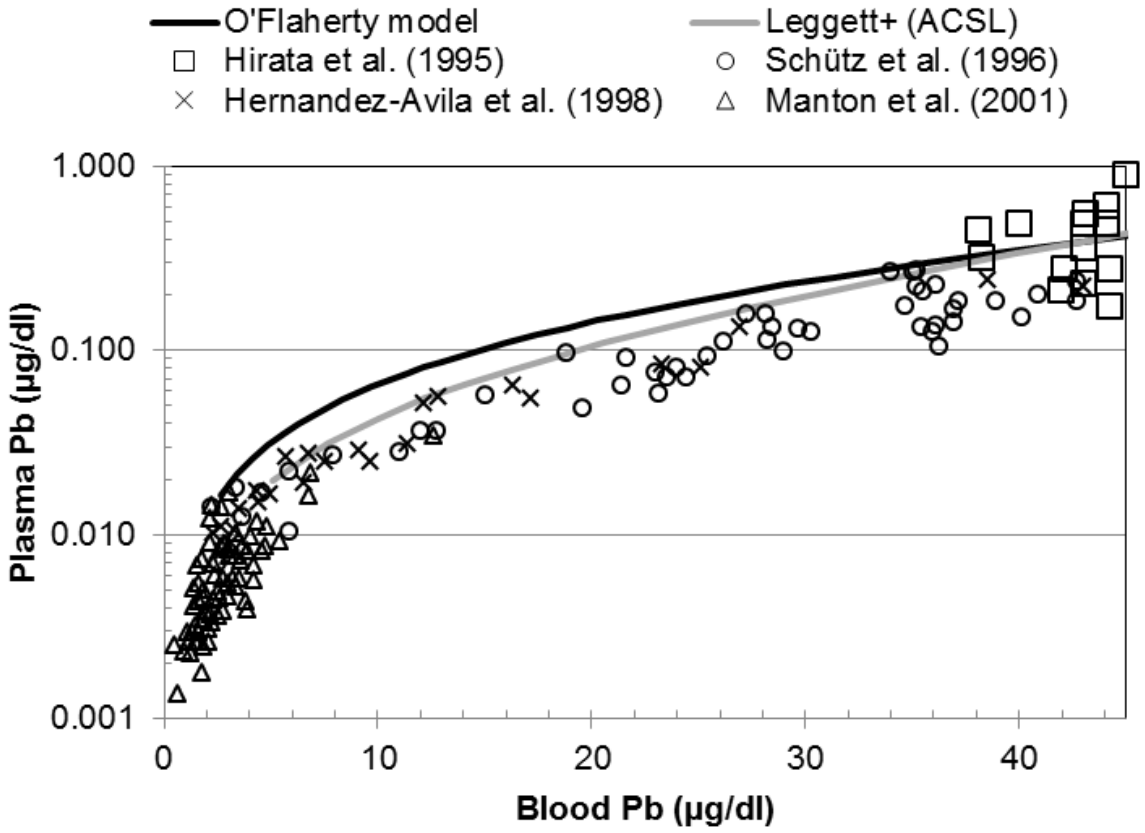


Figure 5. Plasma Pb versus whole blood Pb concentration—predictions from the O'Flaherty model, Leggett+ (ACSL) model, and (upper) data from two worker cohorts considered by Vork et al. (2013) and (lower) data from one worker cohort considered by Vork et al. (2013) from which all relevant data points could be extracted, and three additional data sets from which extraction was >90% complete.

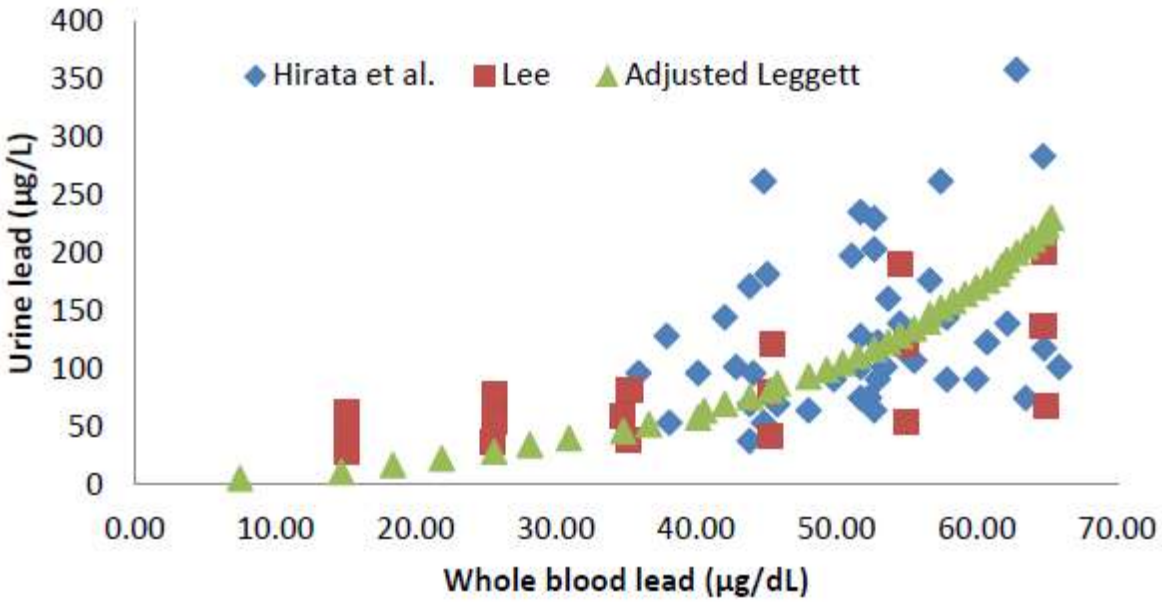


Figure 6. Urine Pb vs. whole blood Pb concentration—predictions from the adjusted Leggett model and data from two worker cohorts (Vork et al., 2013, Figure A-4).

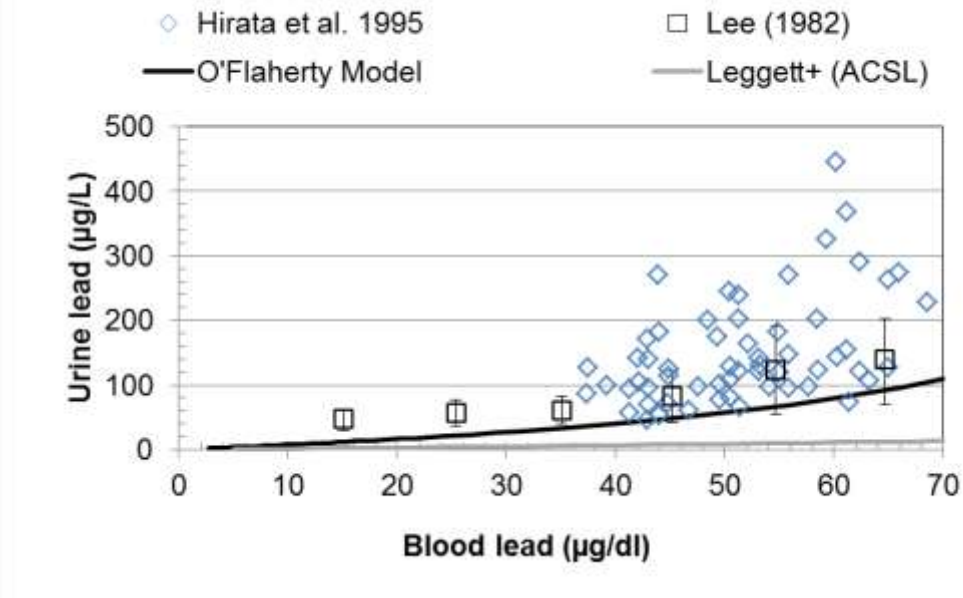


Figure 7. Urine Pb vs. whole blood Pb concentration—predictions from the Leggett+ (ACSL) model, O'Flaherty model, and data from two worker cohorts. Hirata et al. (1995) data are shown individually; Lee (1982) data are depicted as mean ± 1 SD. Numbers of men in each group in Lee (1982) were 27 for BLL from 30.1-40 µg/dl, 38 for 40.1-50 µg/dl, 49 for 50.1-60 µg/dl, and 50 for 60.1-70 µg/dl; a total of 30 workers had <30 µg/dl, but the numbers in the 10-20 and 20.1-30 µg/dl bins was not specified.

Williams et al. (1969)

The Williams et al. (1969) data were used by both Vork et al. (2013) and O'Flaherty (1993) for model validation. Our recreation of the O'Flaherty (1993) simulations (for a 30-year old worker with 10-years of elevated occupational Pb exposure) was evaluated by visual inspection, and determined to be consistent (not shown). Based on tabular data presented by Vork et al. (2013), Table B-3, a plot of BLL vs. workplace air Pb predictions for the Leggett+ (MATLAB) model could be constructed, and was incorporated into a figure depicting the O'Flaherty model and Leggett+ (ACSL) simulations, as well as our digitization of the Williams et al. (1969) data from the original paper (Figure 8). The Leggett+ (ACSL) simulations included two years of pre-occupational adult simulations with initial blood Pb at 20 μg/dl and sufficient background exposure to maintain this level, followed by 20 years of occupational exposure, the occupational duration and beginning BLL specified by Vork et al. (2013) in their Table B-7. Thus the assumptions about work duration differed in the two studies, but based on inspection of time course plots, 10 vs. 20 years of occupational exposure is unlikely to meaningfully affect predictions of BLL (e.g., Vork et al., 2013, Figure 1). The discrepancies between the pairs of digitized estimates were generally small (<2%). The NAMRU-D estimates for the control BLLs (Plastics Department workers) were closer to the published BLLs for these workers (Williams et al., 1969 mean of 28.2 μg/dl, matched by our data extraction, vs. 27.7 μg/dl for Vork et al., 2013). In the Vork et al. (2013) evaluation, however, it should be noted that all subjects with BLL > 60 μg/dl were excluded, leaving only 6 subjects with BLL elevated relative to the controls. This exclusion might be less of a concern if the 13 excluded subjects all had the highest estimated exposures as well, but this was not the case; 6 of the excluded subjects had workplace air exposures that were equal to or lower than that of the most highly-exposed "included" subject. Nonetheless, the models appear to have similar accuracy with respect to prediction of BLLs in this group of workers.

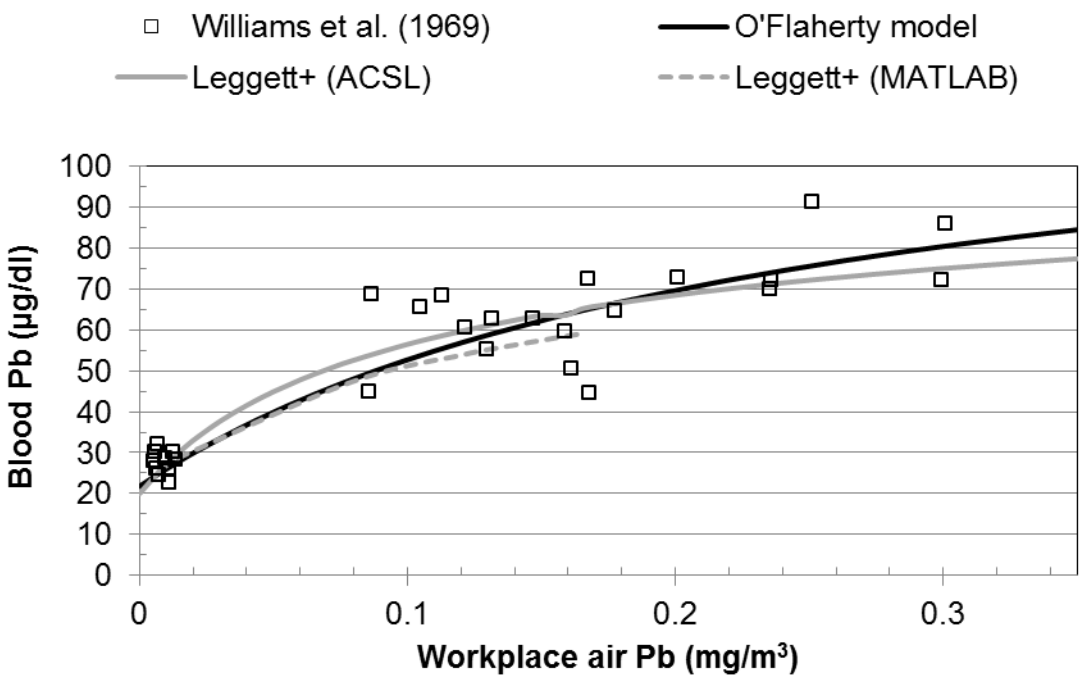


Figure 8. Comparisons of model simulations to experimental data for workers in a lead-acid battery factory (Williams et al., 1969).

Azar et al. (1975)

O'Flaherty (1993) considered the inhalation data of Azar et al. (1975) in developing her Pb model. The ACSL implementation of the Leggett+ model, calibrated for a background BLL of about 13 µg/dl appears to fairly consistently overestimate the measured BLLs in the Azar et al. (1975) study, while the O'Flaherty model provides more accurate predictions.

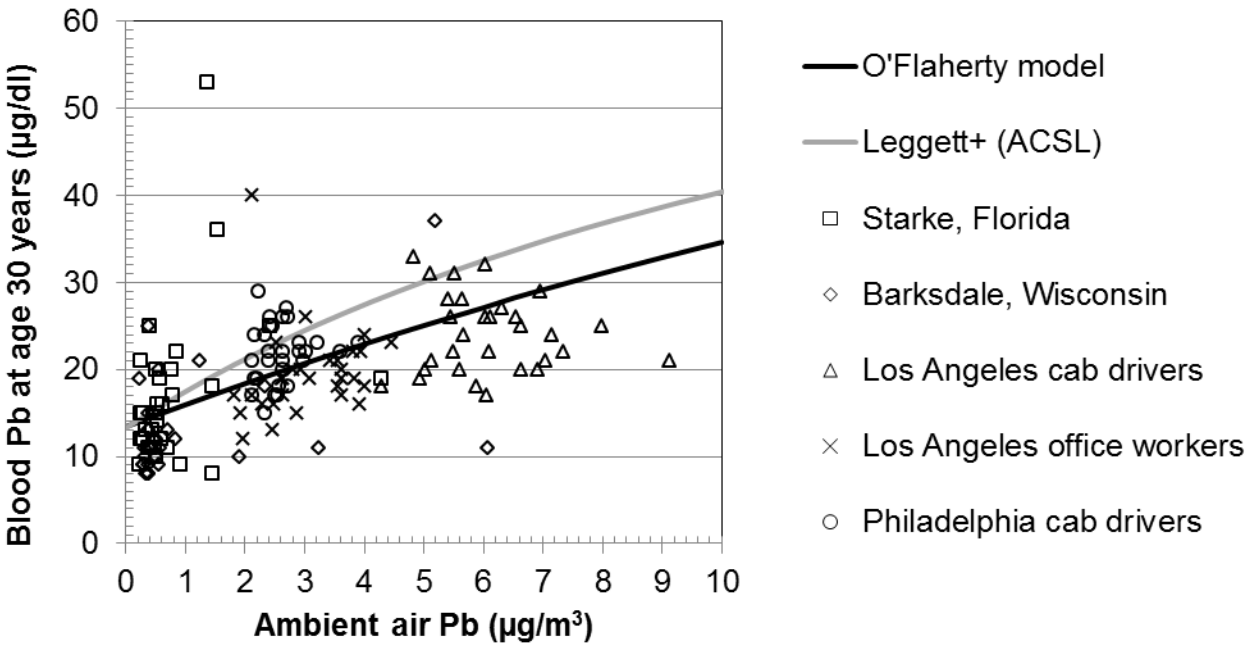


Figure 9. Simulations of 30-year exposure (from birth) to varying levels of ambient air Pb (Azar et al., 1975).

Griffin et al. (1975)

In the study conducted by Griffin et al. (1975), human volunteers (male prisoners) resided in a ward of the prison hospital that had been converted to an exposure chamber with sleeping space for 14. Vork et al. (2013) used pre-exposure blood levels to calibrate an individual's background exposure, and compared a simulated final blood concentration to a measured final value. Based on comparisons of the information in Vork et al. (2013) Table B-8, it appears that Vork et al. (2013) only used the last pre-exposure BLL to calibrate background exposures (typically, 2-3 measurements in a 2-3 week period prior to exposure were available). Also, it appears the final predicted BLL of Vork et al. (2013) was computed based on the total number of exposure days rather than the total number of exposure days prior to the last collected blood sample. In one case, the exposure period was 42 days, but the last BLL sample during exposure was collected 13 days earlier. More commonly the discrepancy was in the range of 3 days difference. For our simulations with the Leggett+ (ACSL) and O'Flaherty models, the background simulation considered all pre-exposure blood samples and the exposure simulation was conducted for precisely the number of days prior to the collection of the last blood sample. In the Leggett+ (MATLAB) model, the average measured less predicted BLL (based on total exposure days) was 0.83 µg/dl. In the Leggett+ (ACSL) model, the difference computed with only exposure days up to the last sample during exposure was 0.72 µg/dl. Using the O'Flaherty model, the difference

was 3.55 µg/dl. The measured vs. simulated values for the Leggett+ (ACSL) and O'Flaherty models are summarized in Figure 10. Vork et al. (2013) only considered the final BLL value during exposure when assessing the quality of the model fit. For the current analysis, time course plots were constructed for all 12 individuals in each phase of the study. These plots are summarized in Figure 11 (3.2 µg/m^3 Pb exposure) and Figure 12 (10.9 µg/m^3 Pb exposure). In general, the models underpredict the data, the O'Flaherty model more so than the Leggett+ (ACSL) model.

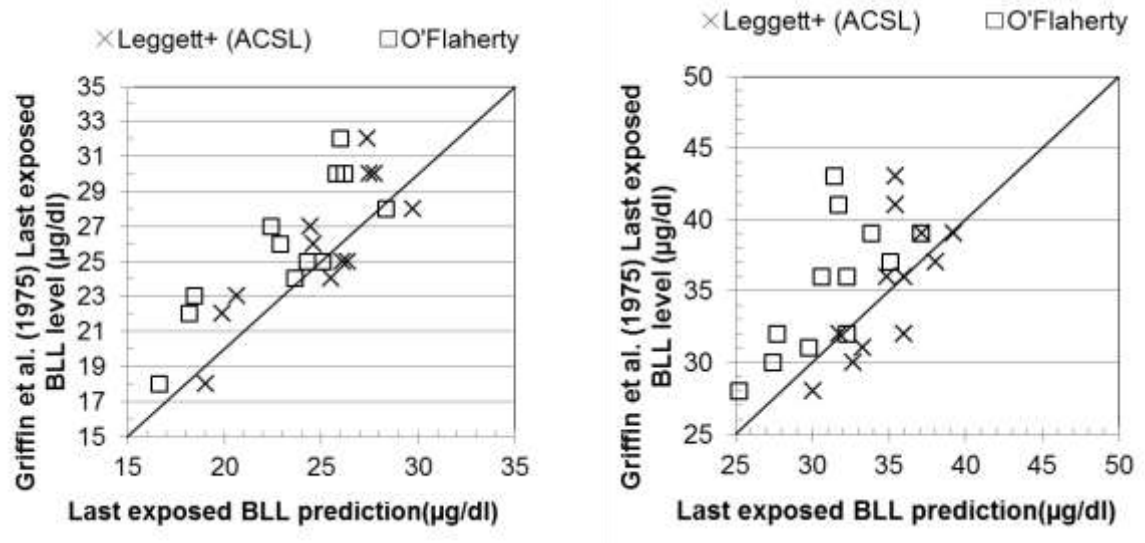
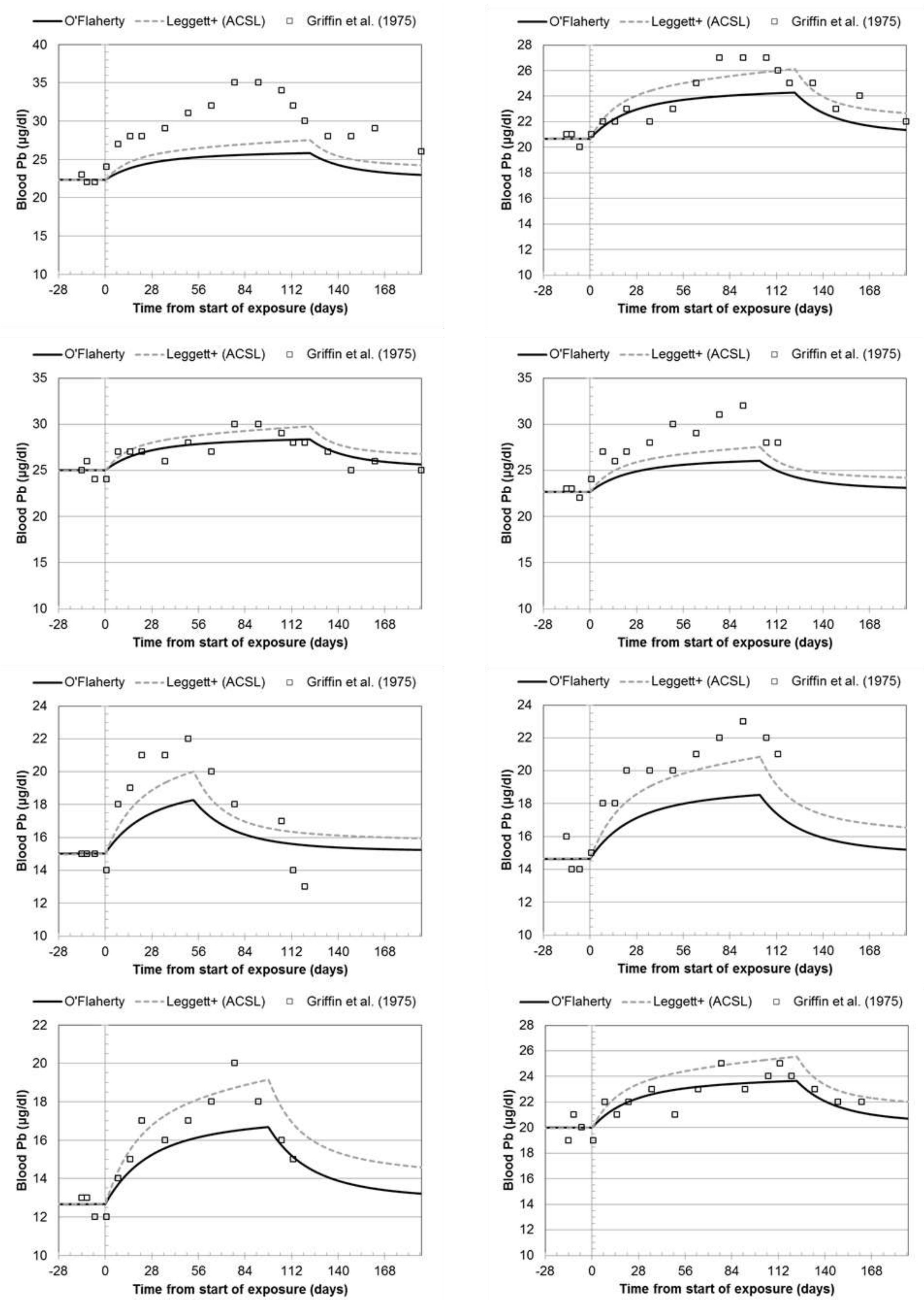


Figure 10. Measured (Griffin et al., 1975) vs. predicted BLL at final blood sample during exposure for men exposed to 3.2 µg/m^3 Pb for 53 to 123 days (left) or 10.9 µg/m^3 Pb for 42 to 123 days (right). The plotted unity line (intercept = 0, slope = 1) represents where all of the comparisons of experiment vs. model predictions would lie if there was perfect agreement between the model and data.


O'Flaherty
Leggett+ (ACSL)
Griffin et al. (1975)
Blood Pb (μg/dl)
Time from start of exposure (days)
-28
0
28
56
84
112
140
168

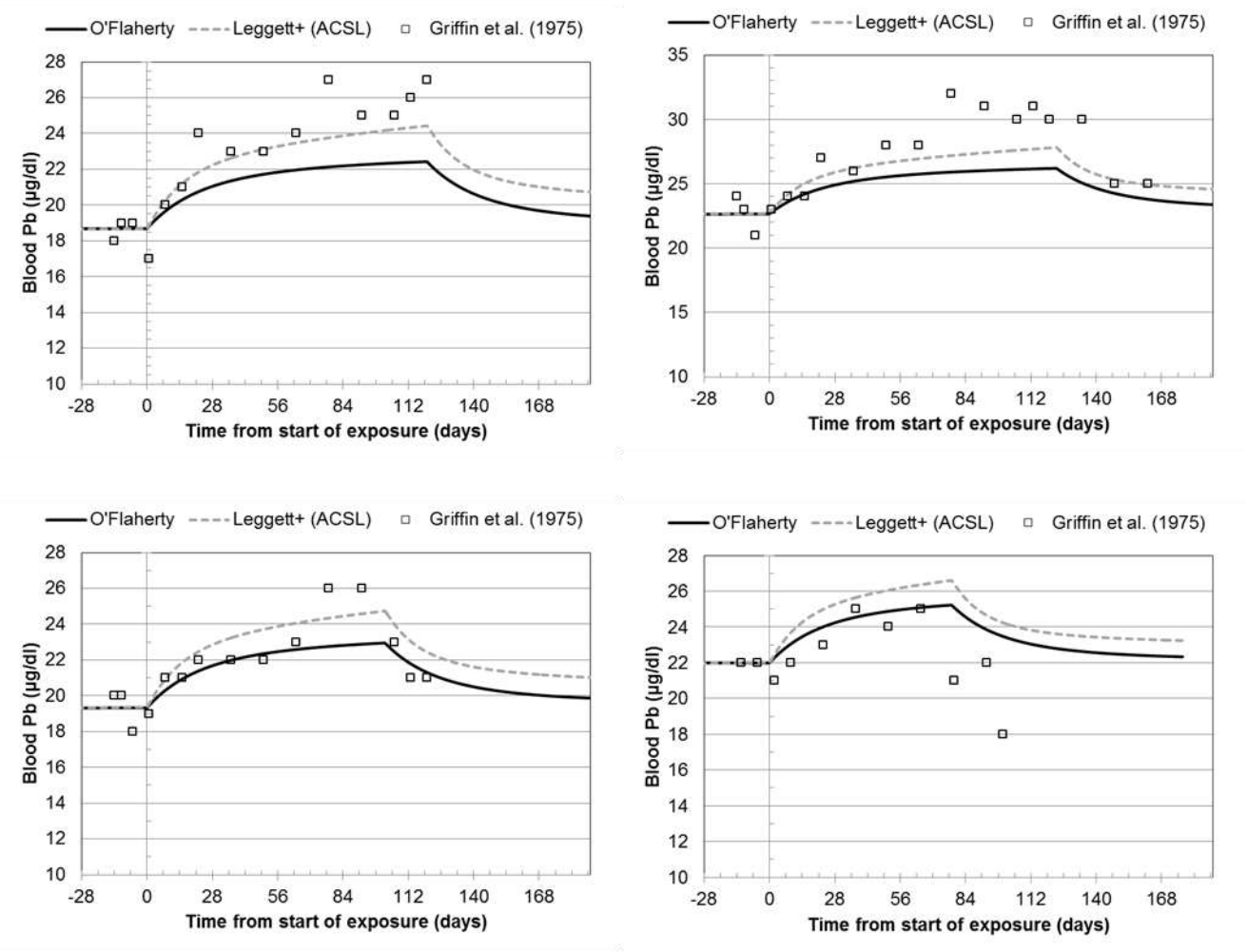
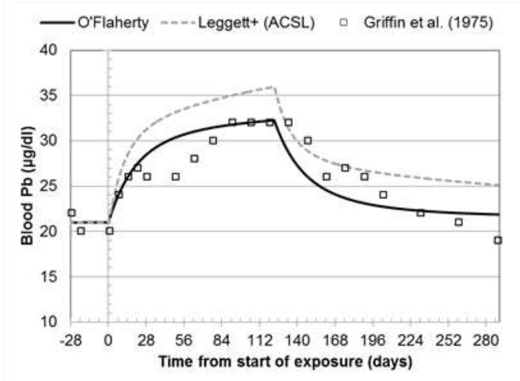
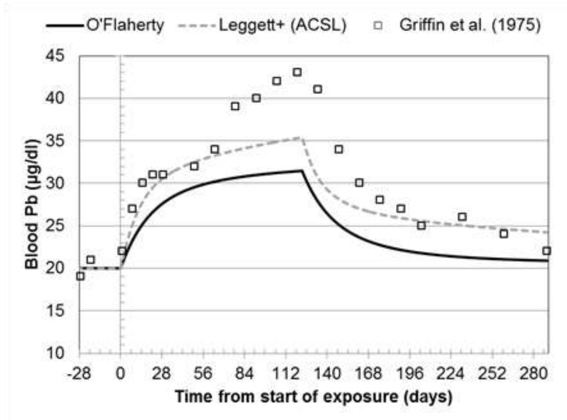
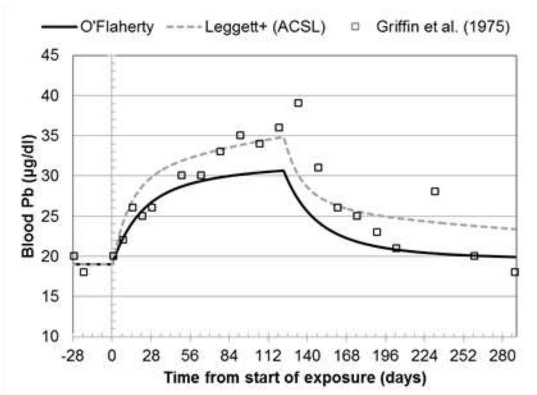
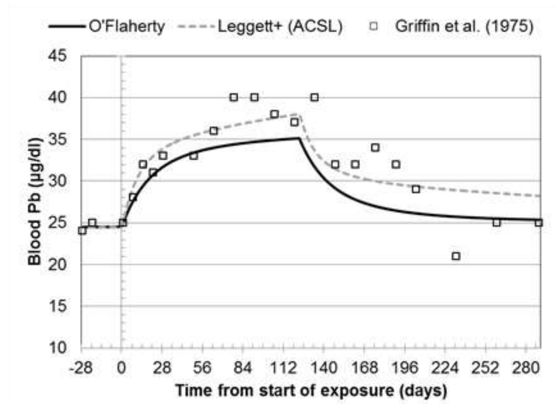


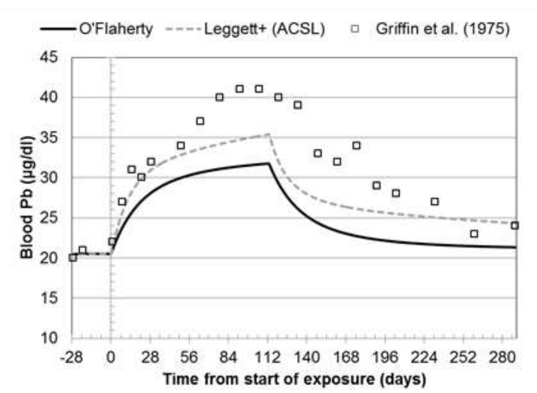
Figure 11. Measured (Griffin et al., 1975) and predicted BLL in human volunteers exposed to 3.2 µg/m^3 Pb for 23 h/d. Left to right, by row: subject ID (assigned by Vork et al. (2013) 32, 33, 34, 35, 37, 38, 39, 310, 311, 312, 313, and 314.

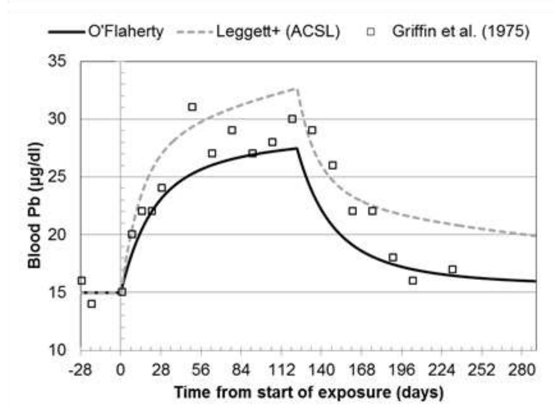

O'Flaherty
Leggett+ (ACSL)
Griffin et al. (1975)
Blood Pb (µg/dl)
10 15 20 25 30 35 40
-28 0 28 56 84 112 140 168 196 224 252 280
Time from start of exposure (days)

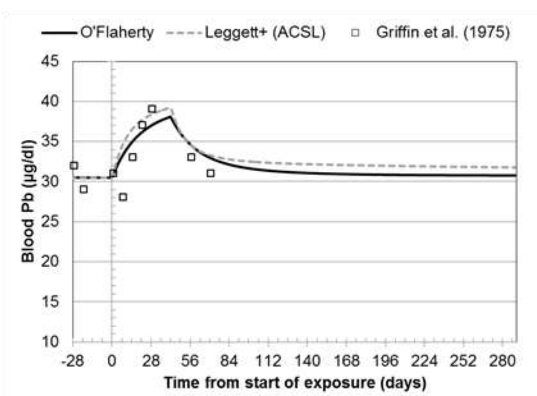

O'Flaherty
Leggett+ (ACSL)
Griffin et al. (1975)
Blood Pb (µg/dl)
10 15 20 25 30 35 40 45
-28 0 28 56 84 112 140 168 196 224 252 280
Time from start of exposure (days)

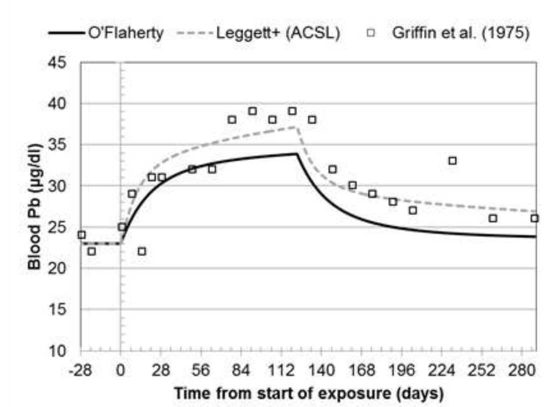

O'Flaherty
Leggett+ (ACSL)
Griffin et al. (1975)
Blood Pb (µg/dl)
10 15 20 25 30 35 40 45
-28 0 28 56 84 112 140 168 196 224 252 280
Time from start of exposure (days)


O'Flaherty
Leggett+ (ACSL)
Griffin et al. (1975)
Blood Pb (µg/dl)
10 15 20 25 30 35 40 45
-28 0 28 56 84 112 140 168 196 224 252 280
Time from start of exposure (days)


O'Flaherty
Leggett+ (ACSL)
Griffin et al. (1975)
Blood Pb (µg/dl)
10 15 20 25 30 35 40 45
-28 0 28 56 84 112 140 168 196 224 252 280
Time from start of exposure (days)


O'Flaherty
Leggett+ (ACSL)
Griffin et al. (1975)
Blood Pb (µg/dl)
10 15 20 25 30 35
-28 0 28 56 84 112 140 168 196 224 252 280
Time from start of exposure (days)


O'Flaherty
Leggett+ (ACSL)
Griffin et al. (1975)
Blood Pb (µg/dl)
10 15 20 25 30 35 40 45
-28 0 28 56 84 112 140 168 196 224 252 280
Time from start of exposure (days)


O'Flaherty
Leggett+ (ACSL)
Griffin et al. (1975)
Blood Pb (µg/dl)
10 15 20 25 30 35 40 45
-28 0 28 56 84 112 140 168 196 224 252 280
Time from start of exposure (days)

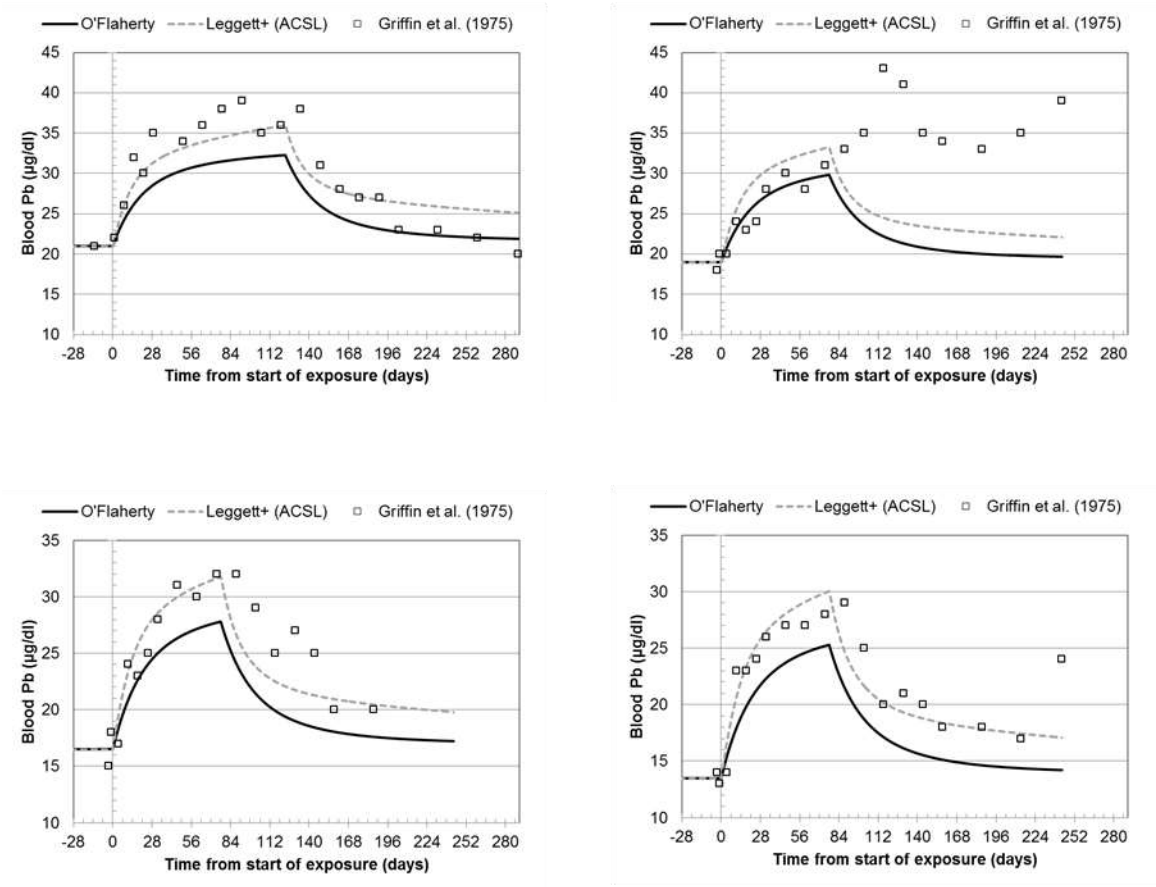


Figure 12. Measured (Griffin et al., 1975) and predicted BLL in human volunteers exposed to 10.9 µg/m^3 Pb for 23 h/d. Left to right, by row: subject ID (assigned by Vork et al. (2013) 317, 318, 320, 321, 322, 323, 326, 327, 328, 329, 330, and 331.

Cools et al (1976)

The men in the Cools et al. (1976) study ingested Pb acetate with sucrose (or a sucrose placebo) in capsule form in a single-blind study. Initially, men in the dosed group (n= 11) ingested 30 µg Pb/kg each day. Once an individual's BLL reached 40 µg/dl, the dosage was decreased to 20, 10, or 0 µg Pb/kg/day as necessary to sustain the BLL at or above 40 µg/dl until the end of the 49-day experiment. O'Flaherty (1993) simulated this variable rate exposure scenario, though the current model code does not appear to include timing commands that would facilitate these simulations. Her results are reproduced below (Figure 13). Vork et al. (2013) did not use these data in model development or validation. Simulation of the entire variable ingestion scenario was too complex for the timing commands built into the model. Two simulations, however, were conducted to assess the ability of the Leggett+ (ACSL) model to predict these data. For the first seven days, all of the dosed men received a Pb dose of 30 µg/kg/day. This scenario was reproduced by simulating 2 years of adult pre-experimental exposure to sufficient Pb to achieve the average BLL measured in control participants (n = 10), followed by one week of 30

µg Pb/kg/day at a bioavailability of 8% (O'Flaherty, 1993). This simulation is shown along with the extracted experimental data (Figure 14). In addition, Cools et al. (1976) noted that the time to reach a BLL of 35 µg/dl ranged from 7 to 40 days, with an average of 15 days. Simulations with the Leggett+ (ACSL) model provide an estimate of 25 days to achieve 35 µg/dl with daily oral dosing of 30 ug/kg/day. Based on these simulations, both models can adequately simulate the Cools et al. (1976) data.

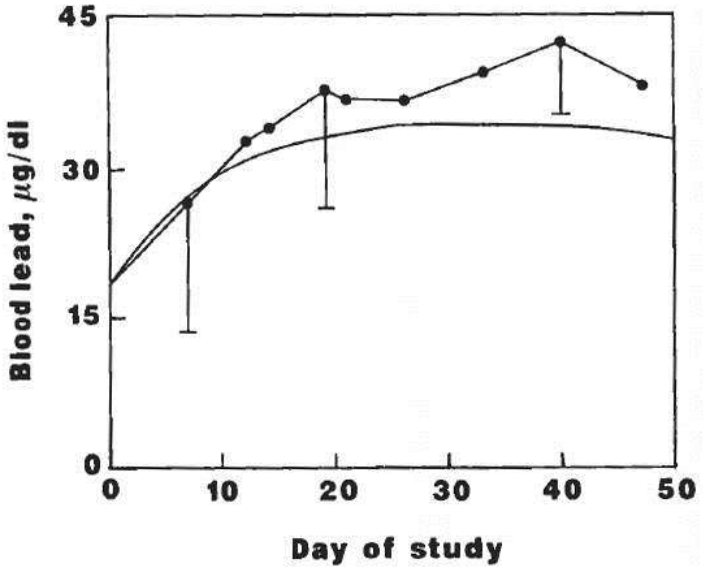


Figure 13. O'Flaherty (1993), Figure 10. Simulation of the experimental conditions of Cools et al. (1976). The smooth line is the simulation for a 25-year old man with variable rates of lead acetate ingestion over a 49-day period. Symbols represent mean values for the dosed group; error bars indicate range for three of the means (n = 10; doses varied among individuals).

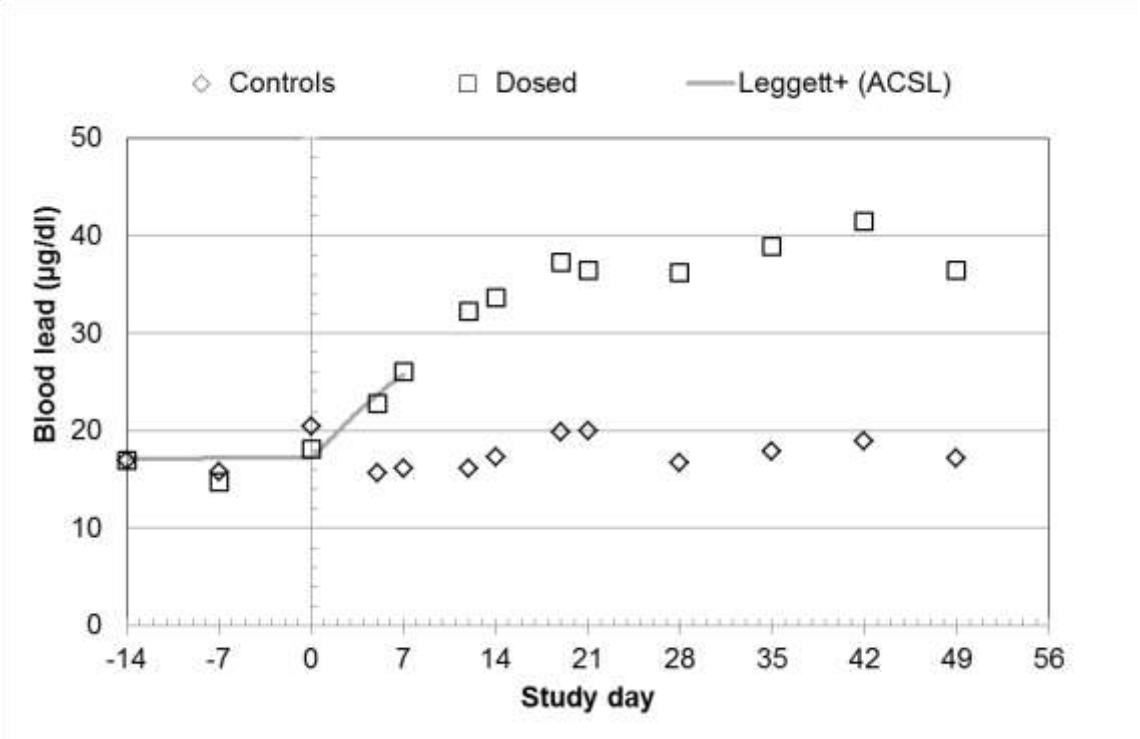


Figure 14. Simulation of the first seven study days of Cools et al. (1976). Symbols represent mean values for the men in the dosed group (n = 11) or control subjects (n =10). During the first seven days, all subjects ingested 30 µg Pb/kg/day; thereafter, individual doses were adjusted to maintain BLL at around 35 µg/dl.

Moore et al. (1977) and Sherlock et al. (1982)

Both Moore et al. (1977) and Sherlock et al. (1982) investigated the relationship between various concentrations of Pb in drinking water and BLL. O'Flaherty (1993) used both of these studies in developing her model. Our attempts to recreate her simulations were not entirely successful. The O'Flaherty model code we obtained incorporates the assumption of ingestion of 2 L of drinking water per day for adults. The paper itself (O'Flaherty, 1993) does not state an adult drinking water ingestion rate. This rate of 2 L/d exceeds the mean rate of 1.227 L/day for adult consumers ≥ 21 years old, but is below the 95th percentile rate for this age group (3.092 L/day) (U.S. EPA, 2011). Our simulations with an adult drinking water ingestion rate of 0.55 L/day yielded closer simulations of published figures than the value built into the model. The study of Moore et al. (1977) was not suitable for simulation with the Leggett+ model because it involved variability in childhood ingestion rates among individuals, which cannot be captured in an adult-only model, and O'Flaherty (1993) assumed the subjects were 20-year old men for her simulations. The Sherlock et al. (1982) study could be simulated (assuming a common drinking water ingestion rate and bioavailability rate for the Leggett+ (ACSL) model) because O'Flaherty (1993) assumed 10 years exposure from age 20-30 years (Figure 15). The Sherlock et al. (1982) data were represented in Figure 15 as a cube-root equation developed by those authors.

Individual data could not be extracted because the information was provided in tabular form with BLL bins of <10 µg/dl, 11-15, 16-20, etc., for ranges of water Pb (<10 µg/dl, 11-99, 100-299, etc.).

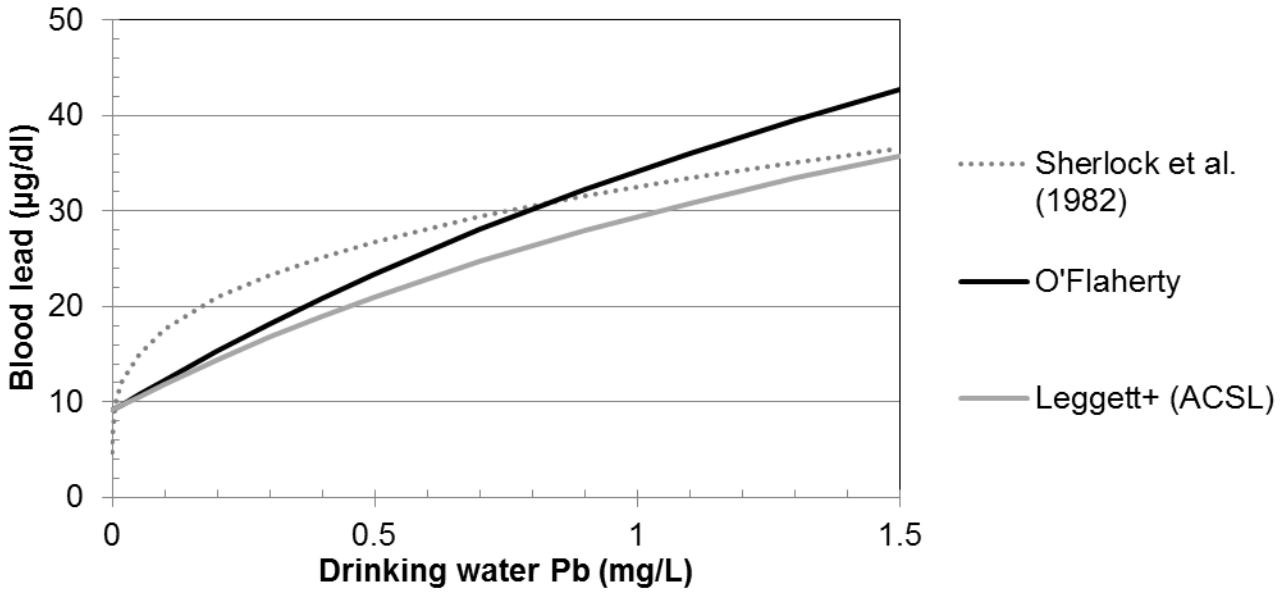


Figure 15. Simulation of the experimental conditions of Sherlock et al. (1982) using pharmacokinetic models for Pb. The Sherlock et al. (1982) are represented by the dashed line, which is the cube root equation the authors selected as an approximation of their data.

Van de Vyver et al. (1988)

O'Flaherty (1993) used the blood and bone (iliac crest) Pb data of Van de Vyver et al. (1988) in the development of her model. Individuals were assumed to have 30 years elevated occupational exposure to airborne Pb. In attempting to reproduce the O'Flaherty (1993) simulations, it was initially assumed that the predicted "bone" values were the model value of skeletal Pb (CSKEL). Upon further evaluation, it was found that using the trabecular bone Pb concentration (TCB, expressed in µg/L in the model) divided by bone density (DBONE, in the model) allowed corresponding figure in O'Flaherty (1993) to be reproduced. For consistency, trabecular bone concentration in Leggett+ (ACSL) was also used as the metric of comparison (Figure 16). Both models do good job of reproducing the bone vs. blood Pb relationship observed by Van de Vyver et al. (1988) in the 10-50 µg/dl BLL range, but the O'Flaherty model has better performance at higher BLLs.

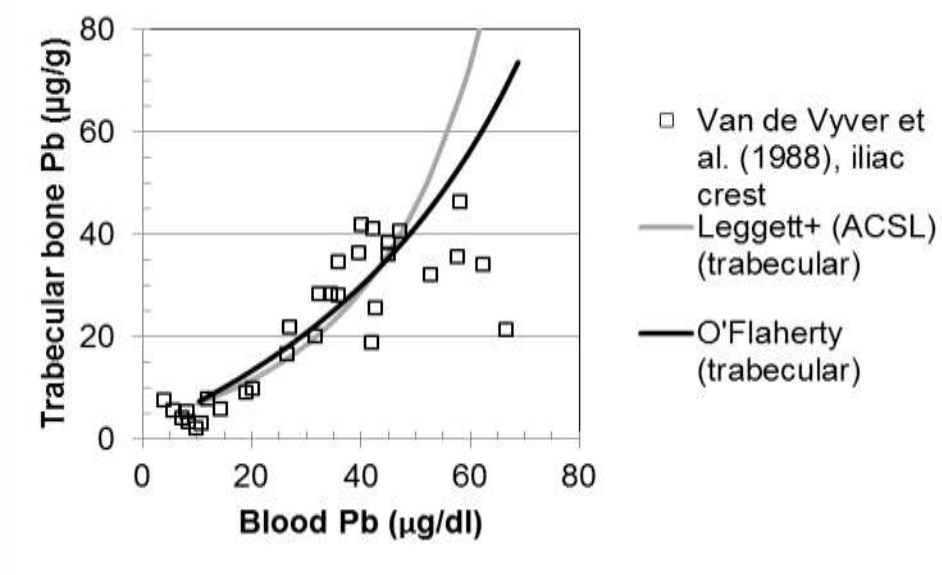


Figure 16. Bone Pb vs. blood Pb in the Van de Vyver et al. (1988) study. O'Flaherty simulation is for a 50 year-old male, exposed for 30 years in the workplace; Leggett+ (ACSL) simulation is for 30 years of elevated adult exposure.

Mass Balance of Absorbed Pb

Vork et al. (2013) do not address the extent to which the Leggett+ model reproduces the observation on the excretion of absorbed Pb via various pathways. In the original Leggett model (Leggett, 1993), the relative rates of excretion by urinary vs. fecal pathways can be estimated from plot curves of excretion rates of injected Pb over time. After an initial distribution phase, the ratio of urinary to fecal excretion (determined by visual inspection) appears to be 2:1 (Leggett, 1993, upper panel of Figure 11). Simulations with the Leggett+ model (both ACSL and MATLAB versions) and O'Flaherty model are summarized in Table 4. The urinary excretion rate for the Leggett+ model was computed using compartmental masses and transfer rates for the two pathways to the bladder, not the predicted urine concentration predictions calculated as described in code provided by Dr. Vork (discussed above). The urine feces ratio in the Leggett+ model was closer to the inverse of the ratio in the original model, with fecal excretion occurring at a rate ~2.4-fold higher than the urinary excretion rate. The O'Flaherty model was used to simulate an adult born in 1970, with model-predicted excretion rates determined at age 45 (i.e., in 2015). The excretion rates add up to the default Pb absorption rate used in Vork, but the O'Flaherty model urine: feces split is 70%: 30%, or ~2.3:1, a ratio similar to the original Leggett (1993) model.

Table 4. Model-predicted steady state Pb excretion rates in adults (absorbed Pb = 1.8 µg/d)

Excretion rate (µg/day)	Leggett+ (ACSL)	Leggett+ (MATLAB)	O'Flaherty
Urine	0.42	0.42	1.23
Feces	1.03	0.99	0.53[a]

Excretion rate (μg/day)	Leggett+ (ACSL)	Leggett+ (MATLAB)	O'Flaherty
Sweat	0.18	0.17	0
Other excreta	0.10	0.094	0
TOTAL	1.73	1.67	1.76

[a]Elimination from liver into feces; does not include unabsorbed, ingested Pb

CONCLUSIONS AND RECOMMENDATIONS

The Leggett+ model (Vork et al., 2013) and the O'Flaherty (1993) model for the disposition of Pb in humans demonstrated similar predictive ability with respect to available data on BLL. This finding is perhaps somewhat surprising given that these models were developed roughly 20 years apart and, for the most part, developed using different data sets. The Leggett+ model tends to do a slightly better job of predicting BLL after inhalation, with the O'Flaherty model doing a better job at predicting Pb in urine and bone. The revisions involved in updating the Leggett model to the Leggett+ model appear to have substantially diverted the excretion of absorbed Pb from the urine to the feces. This observation was originally determined using the ACSL version of the Leggett+ that we generated and was subsequently confirmed using the original MATLAB code.

A limitation of our analysis is that our attempts to recreate some of the Leggett+ (MATLAB) simulations with our Leggett+ (ACSL) model that we developed from the OEHHA code were similar, but not identical. We believe this is primarily due to the use of slightly different assumptions, for example, with respect to simulating background (pre-employment) exposure. Our simulations of mass balance (excretion distribution of systemically absorbed Pb) using the original MATLAB code and ACSL+ version were within 7% of each other.

An important advantage of PBPK modeling (relative to more empirical modeling approaches) is their ability to simulate scenarios for which data are not available, with a reasonable expectation of accuracy. For example, in a physiologically based model, the modeler can incorporate new assumptions when pharmacokinetic data are not available. Examples could include the impact of a different exposure scenario (sporadic or intermittent vs. continuous and chronic) or the impact of physiological differences (e.g., kidney failure). In a non-physiological model, such modifications may be difficult or impossible, because of uncertainty regarding which parameters to modify, and by how much. In this regard, the O'Flaherty model would have to be considered superior to the Leggett+ model. U.S. EPA (2006) previously noted that the O'Flaherty model was more physiologically-based than the Leggett model. The modifications to the Leggett+ model made some moves toward being more physiologically realistic (removal of the blood binding threshold), but largely left the structure unaltered.

The observation that the Leggett+ model parameter changes produced (in our ACSL implementation) the redistribution of excreted Pb from the urine to the feces is of particular concern when it comes to possible population simulations (e.g., Monte Carlo simulation) and raises the question of the physiological consistency/realism of the updated parameters. The

finding that prediction of urine concentrations by OEHHA was not done in a physiologically realistic way (the mass present in a kidney tissue region was used, rather than the transfer rate to the bladder) reinforces doubts about physiological realism of the optimized transfer parameters.

All of the OEHHA (Vork et al., 2013) BLL "percentiles" are estimates based on an assumed lognormal distribution of BLLs rather than Monte Carlo simulations. The distributions are assumed to have a geometric standard deviation (GSD) of 1.6, based on observations in a control (background) population BLL, and supported by other analyses. As a result, the 95^{th} percentile/50^{th} percentile ratio is always 2.2. In the reverse dosimetry calculations (that is, calculating the target exposure for a given blood level), OEHHA assumes the same GSD is applicable to the exposure concentration percentiles. At steady state, BLLb *Vd*k is approximately equal to intake, where BLLb is the background blood Pb concentration, Vd is the volume of distribution, and k is the first order elimination rate. Rearranged, BLLb = (background intake)/(Vd*k); by extension, in highly exposed individuals, BLL = intake/(Vd*k). In the OEHHA approach, all of the variability in BLL must assumed to come from (Vd*k) if BLL (with intake constant) has the same distribution as BLLb. If it is desirable to determine the impact of population variability on BLL as part of establishment of an OEL, variability in parameters describing key physiological processes will necessarily result in variability in BLL. If the real-life key processes in the pharmacokinetic model differ from the processes that are "sensitive" in the model (fecal vs. urinary elimination), the changes in the output cannot be expected to yield accurate predictions when perturbations are made to the input or model parameters. In other words, if the model is getting the "right" answer for the wrong reasons, when the question changes, the potential for the model to give a wrong result is higher for a non-physiological model.

Data exist that contradict the assumption of Vork et al. (2013) that BLL variability in highly exposed individuals is equivalent to the variability in those exposed at background. As previously noted (Table 1), Hattis (1981) and Griffin et al. (1975) report both pre-exposure BLLs and BLLs that reflect elevated exposure in individuals. That is, each group's "pre-exposure data" serve as the controls for the exposed group. The men in the Hattis (1981) study were smelter employees. In the subset of data used for model optimization (n = 47), these men had mean ± standard deviation preemployment BLLs of 20.4 ±7.6 μg/dl (coefficient of variation = 0.37), whereas their pre-strike (employed) BLLs averaged 44.3 ± 8.2 μg/dl (coefficient of variation = 0.18). Griffin et al. (1975) exposed human volunteers to constant, controlled concentrations of Pb for 23 h/d (two studies, with different elevated concentrations). BLL was measured before, during, and after the study. The pre-study BLLs reflect background exposure levels; the last BLL measurement can be used to represent the elevated exposure conditions. Only individuals completing the study are included (n = 12 for each of the two studies). For the higher concentration study, the background BLL (average ± standard deviation) was 20.3 ± 4.5 μg/dl (coefficient of variation = 0.22), and the last measured BLL during exposure in the same individuals averaged 35.3 ± 4.7 μg/dl (coefficient of variation = 0.13). At the lower

concentration, the additional BLL was a smaller percentage of the background BLL, so the diminution of the coefficient of variation was less—a decrease in the coefficient of variation from 0.19 to 0.15 (19.6 ± 3.8 μg/dl background vs. 25.8± 3.9 μg/dl in the exposed group). These data demonstrate empirically that individuals with the same elevated inhalation exposure exhibit less variability in BLL than the same groups of individuals did when they only experienced background exposure. Use of a physiologically-based model to generate estimates of a population distribution of BLL levels is likely to produce smaller and more realistic ratios of the 95^{th} percentile/50^{th} percentile worker BLLs than the Vork et al. (2013) assumption.

Based on considerations of model performance and potential for extrapolation, the author recommends that the DOD strongly consider using the O'Flaherty model in future efforts to guide the DOD Occupational Medicine and Industrial Hygiene communities in their implementation of the USAPHC (2014) guidelines regarding acceptable BLL in Pb-exposed workers.

ACKNOWLEDGMENTS

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